Identification of Network-Based Risk Factors Associated with Gonorrhea

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ABSTRACT

The evolving antimicrobial resistance coupled with a recent increase in incidence highlights the importance of reducing gonococcal transmission. Establishing novel risk factors associated with gonorrhea facilitates the development of appropriate prevention and disease control strategies. Sexual Network Analysis (NA), a novel research technique used to further understand sexually transmitted infections, was used to identify network-based risk factors in a defined region in Ontario, Canada experiencing an increase in the incidence of gonorrhea. Linear network structures were identified as important reservoirs of gonococcal transmission. Additionally, a significant association between a central network position and gonorrhea was observed. The central participants were more likely to be younger, report a greater number of risk factors, engage in anonymous sex, have multiple sex partners in the past six months and have sex with the same sex. The network-based risk factors identified through sexual NA, serving as a method of analyzing local surveillance data, support the development of strategies aimed at reducing gonococcal spread.

KEY WORDS: Gonorrhea, sexually transmitted infections, sexual network analysis, epidemiology, public health

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AMR	Antimicrobial Resistance
CDC	Centers for Disease Control and Prevention
CGSTI	Canadian Guidelines of Sexually Transmitted Infections
CI	Confidence Intervals
CLSI	Clinical Laboratory Standards Institute
DGI	Disseminated Gonococcal Infection
EDR	Extensively-Drug Resistant
ESC	Extended-Spectrum Cephalosporin
GA	Gonococcal Arthritis
GEE	Generalized Estimating Equations
GISP	Gonococcal Isolate Surveillance Project
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HPPA	Health Promotion and Prevention Act
iPHIS	Integrated Public Health Information System
MIC	Minimum Inhibitory Concentration
MOHLTC	Ministry of Health and Long Term Care
MSM	Men who have Sex with Men
MSW	Men who have Sex with Women
NA	Network Analysis
NAAT	Nucleic Acid Amplification Test
NML	National Microbiology Laboratory
NND	Nationally Notifiable Disease
OR	Odds Ratio
O. REG.	Ontario Regulation
OPHS	Ontario Public Health Standards
PHAC	Public Health Agency of Canada
PHO	Public Health Ontario
PHU	Public Health Unit
PID	Pelvic Inflammatory Disease
PIDAC	Provincial Infectious Disease Advisory Committee
ReA	Reactive Arthritis
R_0	Reproductive Number
SES	Socioeconomic Status
STI	Sexually Transmitted Infection
WHO	World Health Organization

CHAPTER I – INTRODUCTION

Gonorrhea is a sexually transmitted infection (STI) caused by the highly adaptable bacterial pathogen *Neisseria gonorrhoeae*. Gonococcal infection develops in both males and females causing urogenital, anogenital, pharyngeal and conjunctival infections.[1] In severe and untreated cases, infection may cause pelvic inflammatory disease (PID) in women with health sequelae including ectopic pregnancy, infertility and chronic pain, while men may suffer from scarring of the urinary tract and less commonly infertility.[1,2] Untreated neonates who acquire gonorrhea through an infected mother commonly suffer from blindness.[3] Moreover, individuals with gonorrhea have an increased risk of transmitting and acquiring human immunodeficiency virus (HIV).[4] The molecular mechanisms hypothesized to enhance the transmission and acquisition of HIV are the increased local expression of viral RNA and loss of mucosal integrity caused by gonorrhea induced local inflammation.[1,3,5]

Antimicrobial resistance (AMR) rapidly developed following the advent of antibiotic treatment for gonococcal infections in the 1930s.[6] Despite routine replacement of first-line treatment recommendations, gonococcal resistance continues to rapidly evolve contributing to the significant health burden caused by the infection.[6] The ability to effectively treat gonorrhea is threatened due to the development of resistance against a variety of antibiotics classes.[6] With the slowing of antibiotic development since the 1970s, the reduced ability to treat gonorrhea with current antimicrobials is a serious concern.[7] The recent emergence of extensively-drug resistant (EDR) strains of *N. gonorrhoeae*

poses a threat of retuning to the early 20th century where gonococcal infections resulted in serious health consequences due to ineffective treatment regimens.[8,9]

Global resurgence of gonorrhea over the past decade combined with the emergence of highly resistant strains, heightens the importance of improving prevention/control strategies.[4] According to the 2008 World Health Organization (WHO) estimates, 106 million new cases of gonorrhea are reported each year globally.[3] The current trends in gonorrhea, however, underestimate the burden of disease due to underreporting and a lack of testing leading to underdiagnosis.[6] An additional one to two cases are estimated for each reported case of gonorrhea worldwide.[10,11] Currently, gonorrhea is the second most common reportable STI following chlamydia in both Canada and the US.[5,12] In Canada, the rates of gonorrhea have steadily increased between 2001 and 2010 with an overall observed 53.4% increase in gonococcal infections.[5] In 2011, 11,397 cases of gonorrhea were reported nationally which translates to 33.4 cases per 100 000 people.[5] In Ontario, which also reports gonorrhea as the second most common reportable STI, there has been a 23.0% (25.5 to 31.4 cases per 100,000) increase in the incidence rates of gonorrhea between 2002 to 2011 with 4196 cases (31.8 cases per 100,000) reported in 2011.[13] The region in Ontario under investigation in the current study is facing an increase in infection evidenced by the fifty percent increase in incidence in the first six months of 2014 compared with the rates in 2013. With the Canadian national cost of gonorrhea and associated health sequelae estimated to range between 30-74 million dollars CAD in 1991, the predicted healthcare cost as a result of resistance and ongoing transmission is expected to increase.[4]

Effective prevention and control of gonorrhea requires an integrated approach involving effective diagnosis and treatment of infected individuals and their sexual partners, screening of high-risk individuals, prevention counselling, use of preventive measures (e.g. condoms) and enhanced surveillance.[6] In order to accurately target, diagnose and treat individuals at risk, a vital focus of prevention/control strategies involves enhanced surveillance and subsequent analysis at a national, provincial and local level.[6] Common limitations of national and provincial surveillance include the inability to achieve a representative sample and a lack of timeliness in the collation, analysis and reporting of gonococcal trends.[6] Analysis of local surveillance however, is able to evaluate important trends in gonococcal resistance and risk factors found in a defined geographic region. The observed variation in sexual behaviour and demographic characteristics between localized populations further identifies the importance of enhancing the analysis of local surveillance data in order to develop the most effective public health prevention/ control interventions.[14] Additionally, analysis of local surveillance data aids in promoting rapid translation of the evidence required to guide timely treatment recommendations, effective screening and prevention/control strategies. With the emerging threat of untreatable gonorrhea, it is especially important to act rapidly when faced with highly resistant gonococcal strains in order to prolong the effectiveness of the currently recommended antibiotics.[6]

A more recent approach in understanding the epidemiology of STIs is described as network theory.[15] Network theory employs sophisticated mathematical models developed to study a specific type of graph representing the relations between discrete entities.[15] Both social[16,17] and sexual[18] network analysis (NA), derived from network

theory, are used to better understand the transmission of STIs.[19] Social NA involves the analysis of the social relationship structure of a given population while sexual NA focuses specifically on the sexual relationships.[20,21]

NA involves the development of networks known as components, which are constructed through the examination of specific social/sexual relationships in a given population.[22] Individuals are represented by nodes while the relationships between individuals are conceptualized by edges between the nodes.[22] Social and sexual NA has recently been used to further the understanding of STI transmission. With respect to sexual networks, the network is developed through the identification of sexually active individuals and their named sexual contacts in order to identify the structures of sexual relationships within a defined population.[19] Contact tracing employed during sexual NA using passive surveillance data involves the identification of all individuals (contacts) who have engaged in sexual activity with an infected individual (case).[23] The success of sexual NA in identifying HIV as an infectious disease generated great interest in widening the scope of infections analyzed using NA.[16] The application of NA in the study of gonorrhea has enhanced the understanding of gonococcal transmission.[14,24-32] Nevertheless, the analysis of gonococcal transmission through social/sexual networks has been applied in a limited number of populations and requires further investigation.

The region under investigation, which has recently faced an increase in gonococcal infections, necessitates enhanced analysis of local surveillance data with the objective of developing effective prevention/control strategies. The persistence of gonorrhea and recent spike in the incidence in the region provides a fruitful research environment where sexual NA, a novel research technique, can be implemented and

assessed as a method of analyzing gonococcal surveillance data. Therefore, the purpose of this study is to identify both network structure characteristics and network positions associated with gonorrhea together with traditional epidemiological risk factor analysis with the objective of providing insights for health promotion and disease control activities.

CHAPTER II – REVIEW OF LITERATURE

The following chapter encompasses four main sections, which were integrated to highlight the gaps in the current knowledge and the rationale for the study. First, a description of gonorrhea and the causative bacterium known as *N. gonorrhoeae* will be presented followed by an overview of the anatomical sites of infection and an explanation of how gonorrhea is transmitted between an infected individual and a susceptible host. Secondly, the epidemiologically determined risk factors associated with gonorrhea including demographic, lifestyle and sexual-partner characteristics will be outlined. The third section of this review will discuss the current global, national and provincial gonococcal surveillance systems. The limitations associated with the surveillance systems will be explained and aid in the support of conducting in-depth analysis of surveillance data at a local level in order to guide effective treatment and public health prevention/control strategies. The fourth section will discuss the core theories related to NA and how this has been applied in the STI literature. The importance of utilizing sexual NA as a local method of analyzing surveillance data aimed at identifying novel risk factors associated with gonorrhea will be demonstrated. Although beyond the scope of this thesis, it was deemed essential to understand the specific molecular mechanisms responsible for the development of infection in the human host, therefore a review of the literature in this area can be found in Appendix A.

2.1 *Neisseria gonorrhoeae*

N. gonorrhoeae, commonly referred to as gonococcus, is an obligate human pathogen and is the causative agent of the STI gonorrhea.[8] *N. gonorrhoeae* is a gram-negative diplococcus aerobic bacterium with remarkable adaptive capabilities which is evidenced by the development of AMR against a variety of antibiotic classes.[8] Gonorrhea is one of the oldest recorded human diseases with case reporting documented in the Book of Leviticus and ancient Chinese writing.[1] The effective development of adaptive mechanisms and virulence factors has enabled the survival of *N. gonorrhoeae* despite a single host.[1]

2.2 Pathogenesis

Gonococcal pathogenesis is not entirely understood due to the lack of an ideal animal model causing difficulties during *in vitro* investigation.[1] The inability to recreate the diverse microenvironments of the human host in which the bacteria colonize, prevents definitive identification of the molecular mechanisms used by *N. gonorrhoeae* to infect various tissues in males and females.[1] Nevertheless, the target tissues and main bacterial surface constituents involved in gonococcal infections have been identified.[1]

Vaginal, anal, and oral sex enables effective bacterial spread from an infected individual to the ideal bacterial niches of *N. gonorrhoeae* in a susceptible human host.[33] The most commonly infected anatomical sites include the urethra, cervix, rectum, oral cavity, pharynx and conjunctiva.[33] The initial step in a bacterial infection involves effective bacterial and host cell adherence.[33] *N. gonorrhoeae* is capable of successfully adhering to host cells and inhabiting numerous epithelial tissues due to the presence and

modification of various bacterial surface structures.[34,35] Two influential surface structures include gonococcal pili and Opacity proteins.[36] Both phase and antigenic variation result in phenotypic heterogeneity in clonal gonococcal populations through changes in surface protein expression.[36] The functional differences of the phenotypically distinct variants enable *N. gonorrhoeae* to colonize various tissues.[37] Additionally, the high-frequency variations aid in host immune evasion and promote cell adhesion, colonization and infection (for a detailed review of the pathogenesis of gonococcal infections see Appendix A).[36]

Binding of both pili and opacity proteins with the specified host cell surface proteins initiatives a signaling cascade responsible for the activation of endocytosis leading to cellular internalization of the bacteria.[1] The internalized bacteria are able to proliferate in the intracellular environment of the epithelial cells.[1] Following proliferation, the gonococci are released and are able to further colonize the mucosal surfaces. Infection of the urethra in males causes the infected cells to release cytokines and chemokines which initiate an intense inflammatory response.[1] The infected female cervical epithelial cells however, do not elicit an inflammatory response as pronounced as males.[1] Consequently, 50-95% of women with a lower genital tract infection are asymptomatic while, 5-10% of male cases are asymptomatic. [1,10,38]

N. gonorrhoeae is able to evade both the host innate and acquired immune system, including complement and antibody host responses, and successfully inhabit the host tissues for prolonged periods of time if the infected individual does not receive appropriate antimicrobial therapy.[1] Prolonged infection commonly leads to ascension of infection and, although less common, disseminated infections.

2.3 Location of Infection

N. gonorrhoeae causes urogenital, anogenital, pharyngeal and conjunctival infections in both men and women. In adults, urogenital infections are the most common with primary manifestation of urethritis (infection of the urethra) and cervicitis (infection of the cervix) in males and females respectively.[1] When symptoms occur in women, they typically present seven to 21 days following infection and are often mild and mistaken for vaginitis or cystitis.[2] The initial signs of urogenital infection in women include pain and burning while urinating, purulent vaginal discharge and vaginal bleeding between periods and following coitus.[2] The onset of symptoms in men develop two to five days following infection and include dysuria, mucopurulent discharge from the urethra and increased urgency and frequency of urination.[2]

An infected mother is likely to vertically transmit the infection through the genital tract to her neonate during birth; 30-50% of exposed infants develop gonococcal ophthalmia neonatorum (gonococcal conjunctivitis).[2,10]

The gonococci from the primary site of infection are able to ascend into the upper female reproductive tract and the epididymis in males.[37] Ascension of the infection is possible due to the ability of Type IV pili to exhibit twitching mobility.[39] The elongation, tethering and retraction of pili enable flagella-independent movement across moist mucosal surfaces.[39]

A lack or delay in treatment of urogenital gonorrhea in women is common due to the frequency of asymptomatic infections (50-95% of cases) and has the ability to cause serious sequelae.[38] The ascension of infection from the cervix causes PID, which is an infection of the soft tissue of the upper female genital tract structures causing

endometritis, salpingitis, oophoritis and pelvic peritonitis.[10] Approximately 10-20% of women with untreated gonococcal cervicitis develop PID, which can lead to ovarian abscess, tubal factor infertility and ectopic pregnancy.[10,40] The ascension of infection in males is less common and results in epididymitis causing testicular pain, swelling and fever.[2] In rare or untreated cases ascension of gonococcal infections in males can lead to scarring of the urinary tract and infertility.[5]

Rectal infection leading to proctitis occurs in both males and females and is the most common in individuals who engage in receptive anal intercourse.[10] The female anatomy facilitates transfer of infectious secretions from the endocervix to the rectum causing concurrent infection in 30-60% of infected females.[10,41] Proctitis in females is commonly asymptomatic while symptoms are displayed in 50% of males.[10,42] Symptoms in both sexes include pain, purulent discharge, constipation, tenesmus and painful bowel movements.[2,10]

Gonococcal pharyngitis is transmitted through oral sex with an infected individual.[10] In both men and women 60% of cases are asymptomatic however, an asymptomatic individual maintains the ability to spread the infection to their sexual partners.[10] Gonococcal pharyngitis in the absence of infection in another site is rare.[2] Symptomatic females and males may present with symptoms of a sore throat and cervical lymphadenopathy involving inflammation of the lymph nodes in the head and neck.[2] Gonococcal conjunctivitis in adults is most commonly caused by autoinoculation.[10]

Disseminated gonococcal infection (DGI) occurs in 0.1-3% of untreated gonorrhea cases.[1,2,10,43,44] Gonococcal arthritis (GA) develops in 42-85% of patients who acquire DGI.[44] Reactive arthritis (ReA), formally known as Reiter's syndrome, may also

develop following a gonococcal infection however, is more commonly associated with chlamydial infections.[45] Both forms of arthritis are caused by the haematogenous dissemination of *N. gonorrhoeae* from the primary sexually acquired mucosal infection to various joints. In approximately 50% of DGI cases with GA, *N. gonorrhoeae* can be cultured from the blood and synovial fluid indicating a direct bacterial involvement.[44] Notable differences between GA and ReA exist in the characteristics of the high-risk population, site of infection and accompanying clinical symptoms. ReA is most common in young males and individuals who test positive for the human leukocyte antigen-B27 whereas the risk of GA increases in women and individuals with complement deficiencies which impairs serum bactericidal activity.[43] The risk of GA increases in women due to the likelihood of asymptomatic infections leading to a delay in therapy.[43] Additionally, a female is at greater risk of DGI during early pregnancy and menstruation due to changes in the PH of the vagina and cervical mucosa, which favours bacterial growth and exposure of the endometrium to submucosal vessels facilitating haematogenous spread.[44] ReA usually presents asymmetrically in the lower extremities[45] while GA develops in the wrists, hands and knees.[43] Dermatitis, tenosynovitis and pustules with an erythematous base commonly accompany GA.[45]

In addition to GA, DGI can also cause hepatitis (Fitz Hugh-Curtis syndrome), endocarditis, myocarditis, meningitis, pyomyositis and adult respiratory syndrome.[3,10,44] Mortality rates caused by gonorrhea are low, however, fatalities may arise as a result of untreated infection leading to DGI.[46]

2.4 Transmission

The primary mode of gonorrhea acquisition is through sexual contact including vaginal, anal and oral sex. Sexual activity permits the bacteria in colonized mucosa of an infected individual to spread to a susceptible host. Ejaculation is not necessary for transmission to occur.[40] The duration of infectivity for bacterial infections is dependent on the incubation period of a particular pathogen and probability that the infected individuals are symptomatic and treated.[26] The incubation period of urethral infection caused by *N. gonorrhoeae* in men is two to five days while urogenital infections in women have an incubation period of seven to 21 days.[2] The majority of men (90-95%) become symptomatic between two to five days of infection whereas this proportion is much lower in woman.[26] The period of infectivity in symptomatic women and men is three to 45 days and three to 30 days respectively.[47] Asymptomatic women and men have an extended infectious period of three to12 months and three to six months respectively.[10,47]

Gonococcal infection is more likely to spread from an infected male to a female sexual counterpart during vaginal intercourse compared with female to male spread. In a single sexual encounter 50-90% of women will acquire the infection from an infected male compared with 20-25% of males who develop gonorrhea as a result of a single sexual encounter with an infected female.[40,46] The variation in risk can be attributed to the purulent exudate commonly exhibited in males suffering from gonococcal urethritis and the large concentration of gonococci spread to women following ejaculation.[10,40] The gonococcal inoculum delivered through ejaculation, independent of semen volume, is 100 times greater than the inoculum encountered by the male urethra during vaginal sex.[46] Furthermore, the pathogenic bacteria are in contact with the lower female genital tract for

an extended period of time increasing the likelihood of transmission.[1] Transmissibility data for both pharyngeal and rectal gonococcal infections are limited however, recent analysis of bacterial load in rectal and pharyngeal infections suggests an increased transmissibility during rectal intercourse compared with oral sex. This hypothesis is strengthened by the significantly higher bacterial load found in symptomatic proctitis compared with the commonly asymptomatic pharyngeal infection.[48] The majority of gonococcal infections are transmitted from asymptomatic individuals to susceptible sexual partners.[46]

Vertical gonococcal transmission occurs as neonates come in direct contact with an infected cervix during delivery.[10] Intrapartum transmission occurs in 30-50% of neonates born to a mother with untreated gonococcal cervicitis.[49] In Canada all females are screened at the first prenatal visit for a number of STIs including gonorrhea.[50] Women who are considered at high-risk of infection undergo repeat screening each trimester.[50] In summary, the ease of transmission and high morbidity caused by gonococcal infections necessities accurate and timely surveillance of gonorrhea cases in order to identify risk factors and develop effective prevention/control strategies.

2.5 Risk Factors

2.5.1 Risk Factor Reporting in Canada

The Canadian Guidelines of Sexually Transmitted Infections (CGSTI) lists the following individual risk factors for gonorrhea: individuals who have had sexual contact with a person with a confirmed or suspected gonococcal infection, individuals who have had unprotected sex with a resident of an area with high gonorrhea burden and/or high-risk of

AMR, individuals with a history of previous gonococcal infection, individuals with a history of other STIs including HIV, sex workers and their sexual partners, sexually active youth less than 25 years of age, street-involved youth and other homeless populations, men who have unprotected sex with men and individuals who have had sex with multiple partners.[50]

In 2013, Public Health Ontario (PHO) identified the following risk factors as particularly important in Ontario: sexually active women less than 25 years of age since they represent 65% of infections in women in Ontario and sexually active men who have sex with men (MSM) since they represent a significant portion of all gonorrhea diagnosis in men.[13] Additionally, the most recent report (2011) by the Ministry of Health and Long Term Care (MOHLTC) using the integrated Public Health Information System (iPHIS) database identified failure to use a condom (74.0%), having sex with the opposite sex (37.0%), having more than one sexual contact in the past six months (25.0%), having sex with the same sex (24.6%) and having a new partner in the last 2 months (17.2%) as the most frequently reported risk factors for acquiring gonococcal infections among gonorrhea cases.[13]

The abovementioned risk factors in addition to commonly discussed risk factors found in the literature have been divided into the following categories including demographic, lifestyle and partner characteristics, and will be discussed. Risk factors specific to gonococcal reinfection will be discussed separately. Identifying and understanding the risk factors of gonorrhea is required in order to effectively develop prevention/control strategies. The investigation of local risk factors is of particular interest in order to develop regionally specific prevention/control strategies. Although

risk factors are reported in many studies, limited research provides statistical evidence relating specific risk factors and the risk/odds of acquiring gonococcal infections. Consequently, heavy reliance was placed on two studies conducted in San Francisco, US[51] and Alberta, Canada[4] which included the statistical significance for a number of risk factors and their association with gonorrhea.

2.5.2 Demographic Risk Factors

2.5.2.1 Age and Sex

Young adults and adolescents are currently at the greatest risk of gonorrhea in both Canada and the US. Over the last decade, the high-risk age group has decreased from individuals greater than 30 years for both sexes to teenage females between the ages of 15-19 and young adult males between the ages of 20-24.[46] Consistent with US reports,[52] in Canada in 2011 the majority of gonococcal infections (70.5%) were reported in individuals less than 30 years of age.[5] Highest reported rates for females were those between 15-19 years (147.0 per 100 000) followed by those between the ages of 20-24 (133.8 per 100 000).[5] In males, the highest rates were reported in those 20-24 (134.5 per 100 000) followed by those between 25-29 years (109.9 per 100 000).[5] Conversely, in Ontario both males and females had the highest prevalence of gonorrhea in the 20-24 age category.[13] Nevertheless, the highest incidence rate in 2011 for males was observed in individuals greater than 25 and in females less than 25, which aligns with the national findings.[13] In 2011 in Ontario, the rate of gonorrhea was higher for males (36.33 male cases per 100,000) when compared with females (26.46 female cases per 100,000).[13]

2.5.2.2 Race/Ethnicity

Surveillance data and a number of studies have demonstrated an increased risk of infection in black individuals in both Canada and the US.[4,51,53] Study findings consistently identify an increased odds of infection in black individuals across various populations. In a San Francisco, US based case-control study an increased odds of infection in black males (OR = 5.7, 95% CI = 2.0, 16.7) and females (OR = 2.6, 95% CI = 1.05, 6.3) was found.[51] A Canadian based retrospective cohort confirms these findings, as the risk of reinfection in black individuals compared with white cases was significantly greater (RR = 3.31, 95% CI = 2.27, 4.81).[4] The increased infection rate has previously been explained by inequitable access to health care and socioeconomic disparities.[46] Nevertheless, after controlling for socioeconomic status (SES), medical access and risky sexual behaviour, studies reveal an elevated risk in black individuals.[46,54-57] A lack of biological evidence for increased susceptibility has influenced interest in addressing the disparity through sexual NA.[54]

2.5.2.3 Socioeconomic Status

Low SES status has been identified as a significant risk factor for gonorrhea.[57] Spatial patterning of gonorrhea cases in Calgary (Alberta, Canada), Winnipeg (Manitoba, Canada) and Baltimore (Maryland, US) revealed similar trends in the clustering of high (core areas), intermediate (adjacent areas) and low (peripheral areas) prevalence based on SES.[58-60] Core areas were clustered in the centre of the mapped area and had the lowest SES. The adjacent areas were found on the edge of the core areas while the peripheral areas had the highest SES and were outside of both the core and adjacent areas.[58-60]

Correlation between high/low SES variables and gonorrhea rates in Calgary revealed a moderate to strong negative correlation between areas with high gonorrhea rates and high SES variables including being married (r = -0.749), living in a detached home (r = -0.632) and having a median household income (r = -0.674).[58] The combined findings illustrate the association between individuals living in low SES areas and an increase in the risk of gonococcal infection. Localized sexual networks are believed to be the cause of the geographic clustering of gonorrhea cases and require further investigation.[31,59] A common observation in core areas with low SES (defined by household income) is the increased number of ethnicities, primarily black individuals, who are independently identified as a population with greater risk of infection. With this consideration in mind, Rice *et al*. found a strong inverse correlation between gonorrhea incidence and SES in Seattle, US while accounting for race/ethnicity.[61]

Common variables observed in low SES areas including low academic achievement, unemployment, single parent homes, limited access to health/behavioural intervention resources, prostitution and illicit drug use, influence risky sexual and health behaviours which increase the spread of gonorrhea in core areas.[61] Common health behaviours facilitating the persistence of increased gonococcal transmission in low SES areas include the inability to recognize symptoms of gonorrhea, delay in seeking treatment following the onset of symptoms, continued sexual activity despite the onset of symptoms, a lack or delay in notifying sexual partners and noncompliance with therapy.[61]

2.5.3 Lifestyle Risk Factors

2.5.3.1 Sexual Behaviour Characteristics

The obligate human pathogen *N. gonorrhoeae* is incapable of infecting nonhuman hosts and cannot survive outside the human body.[46] Consequently, the sole means of transmission involves deliberate sexual relations between individuals. The examination of sexual encounters provides insight into the transmission dynamics of gonorrhea and has influenced the identification of a number of high-risk sexual behaviours responsible for the persistence of infection. Gonorrhea is spread through the mucosal secretions of the urogenital, anal and pharyngeal human anatomical sites therefore, condoms serve as a protective barrier against the transmission of infection.[62] A vast number of studies have evaluated the effectiveness of condom use in the prevention of gonorrhea transmission.[62] The majority of studies included in a recent systematic review established that condom use leads to a decrease in the spread of gonococcal infection.[62] Additional risk factors include early onset of sexual activity,[57,61] a greater number of sexual partners,[51,57,63] increased rate of partner change,[57] non-monogamous relationships[51] and anonymous sex.[51]

2.5.3.2 Men who have Sex with Men

MSM remain at an increased risk of infection compared with men who have sex with women (MSW) despite the population being studied. Gonorrhea in MSM increased in the 1970s during the gay liberation movement followed by a sharp decline during the early 1980s shortly after the introduction of HIV/acquired immunodeficiency syndrome (AIDS).[46] The prevalence of HIV/AIDs in MSM and devastating sequelae influenced

changes in sexual behaviour, which protected men against both HIV/AIDs and other STIs.[46] Resurgence in gonorrhea in MSM has been observed since 1996 and is believed to be associated with the improvements and availability of highly active antiretroviral therapy (HAART).[64] The perception of HIV/AIDs has shifted from an infection with fatal consequences to a manageable chronic disease.[4,46] An increase in risky sexual behaviour in MSM has been reported following the availability of HAART in 1996 in the US, Canada, Europe and Australia.[65] Evaluation of the data collected by the Centers for Disease Control and Prevention (CDC) Gonococcal Isolate Surveillance Project (GISP) identified MSM as being primarily older, non-Hispanic white men who were more likely to have had a previous gonococcal infection.[66] Common sexual behaviours observed in MSM include attendance at bathhouses, sex with anonymous partners and unprotected anal intercourse.[64,66]

Comparisons between gonorrhea rates in MSM and MSW in the largest STI clinic in Denver (Colorado, US) during two six year periods (1990-1995 & 1996-2001) revealed a significant increase in gonococcal infections between the time periods and a consistently higher rate of gonorrhea in MSM.[64] These findings are consistent with a number of studies examining the risk of infection and reinfection in MSM in various US States, Canada and Europe.[4,56,66,67] The CDC has reported a steady increase in gonorrhea rates in MSM at all anatomical sites between 1999 and 2005.[65]

2.5.3.3 Marital Status

Gonorrhea cases are most commonly reported in never-married males and females compared with married, common law, divorced, separated and widowed individuals.[4,61]

Cohen *et al.* examined the association between married individuals and gonorrhea rates and identified a moderate negative correlation (r = -0.588).[68]

2.5.3.4 Prostitution

Commercial sex workers (i.e., individuals who exchange sex for money, drugs and gifts) are at a higher risk of infection compared with the general population due to the nature of prostitution and subsequently act as high frequency transmitters of gonorrhea.[69] Commonly observed risky sexual and health behaviours among commercial sex workers include lack of condom use, multiple sex partners, previous infection and failure to receive treatment following the onset of symptoms.[69] Female commercial sex workers have higher gonorrhea rates compared with non-sex workers in both the general[69,70] and incarcerated population.[46,70,71]

2.5.3.5 Incarceration

Incarceration is a marker for increased gonorrhea risk in both adult and adolescent populations. Gonorrhea rates in incarcerated males and females range from 0.1-32% and 0.2-17% respectively, across the US.[71] The odds of infection were approximately three times greater (OR = 3.3, 95% CI =1.04,10.4) in men who were recently incarcerated compared to males in the general population in a case-control study conducted in San Francisco, US.[51] In Alabama, a similar increase in gonorrhea risk was observed in male detained adolescents (14-18 years).[72-74] In addition to the high prevalence of gonorrhea, the male youths reported common risky sexual behaviours including early onset of sexual intercourse, older sexual partners during first intercourse, multiple lifetime sexual

partners and unprotected sex.[72,74] Additional risk factors included low SES, illicit drug use and poor access to medical care.[73] The risky sexual behaviours and additional risk factors reported in these studies are significantly greater than those in males between 15-19 years of age in the general population.[73]

2.5.3.6 Homelessness and Street-Involved Youth

Both youth and adults defined as homeless face barriers to healthcare services, which negatively impacts the timely treatment of gonorrhea.[75,76] Despite universal healthcare insurance in Canada, many homeless individuals do not have proof of coverage because their identification has been lost or stolen.[76] Additionally, the challenges of daily survival outweigh the importance of seeking medical care for conditions perceived to be minor such as the onset of symptoms caused by gonorrhea.[75]

An additional concern with the homeless population is the risky sexual behaviour reported in many street-involved youth (14-25 years).[75] Sexual risk factors reported in street youth include multiple sex partners, early sexual intercourse, unprotected sex, prostitution and sex for survival (i.e., sex in exchange for food, shelter and drugs).[75,77] In Montreal, Canada the majority of street youth reported sexual activity with an average of 11 sexual partners and 25% of street youth engaged in prostitution.[66] Of the sexually active youth, reported condom use was 2.3% and 14.7% for females and males respectively.[66] Additional risk facts reported in street youth include recent incarceration and illicit drug and alcohol use.[78] Illicit drug use is associated with an increase in risky sexual behaviour.[76] Similar rates of sexual activity and reported risky sexual behaviours were observed in Denver, San Francisco and New York.[77] A convenience sample of

homeless youth (16-20 years) in Texas, US identified 25% of participants having a previous infection with gonorrhea.[79] Although, gonorrhea rates in homeless and street youth vary by population,[78,80] risky sexual behaviours remain common practice increasing the likelihood of transmission and acquisition.[78,80] When coupled with risky health behaviours including a delay or lack of treatment, gonococcal infections are easily maintained within homeless populations.

2.5.4 Partner Characteristics

The demographic and behavioural characteristics of an individual's sexual partner have been shown to increase STI rates. The disproportionate prevalence of gonorrhea between adolescent black males and females underscores the role sexual partner characteristics play in the transmission of infection.[81] Adolescent females who are black in the US have twice the incidence of gonorrhea despite increased risky sexual behaviour observed in males.[81] In attempts to explain the unexpected incidence rates, a cross-sectional study conducted in San Francisco, US found that black females with a higher rate of gonococcal infection, compared with males exhibiting high risk sexual behaviour, were significantly more likely to be involved in a partnership with older (OR = 1.48, 95% CI, 1.08, 2.03) and previously incarcerated (OR = 1.86, 95% CI = 1.50, 2.29) males and less likely to have non-black partners (OR = 0.63, 95% CI = 0.51, 0.77).[81] The significant association between a recently incarcerated partner (OR = 6.56, 95% CI = 1.77, 24.27) and STI diagnosis and the increased odds of females having an incarnated sexual partner suggest that the sex differences in gonorrhea rates can be explained by partner characteristics of the infected females.[81]

Similarly, an adult based case-control study conducted in San Francisco found that having a black (OR = 8.3, 95% CI: 3.0, 23.3) or incarcerated (OR = 10.4, 95% CI = 2.0, 55.5) partner were amongst the most influential risk factors for gonococcal infection in women.[51] Independent analysis of the impact of race/ethnicity demonstrated that having a black partner (OR = 8.3 95% CI = 3.0, 23.3) had a stronger association with gonorrhea compared with being a black female (OR = 2.6, 95% CI = 1.05, 6.3).[51] The tendency for women to select black partners,[32] an race/ethnicity with the highest gonorrhea rates,[46] aids in the explanation of gonorrhea acquisition in women with few STI risk behaviours.[51] The role partner characteristics have on sexual behaviour and undesired consequences has helped establish the importance of analyzing sexual networks when identifying risk factors.[82-86]

2.5.5 Risk Factors for Reinfection

Reinfection of gonorrhea contributes to the persistence of infection in a given geographic location.[4,87] A retrospective cohort conducted in Alberta, Canada found that a small percentage of the sample population (8%) who were reinfected with gonorrhea were responsible for a large proportion of the overall incidence of gonorrhea (16%) in the defined study population.[4] Several studies support these findings in various populations.[87-89] Risk factors for reinfection in Alberta included individuals who were black (RR = 3.31, 95% CI: 2.27, 4.81), Aboriginal (RR = 2.63, 95% CI = 1.96, 3.56) and those who were homo/bi-sexual (RR = 2.05, 95% CI = 1.40, 3.02). Additionally, being married (RR = 0.33, 95% CI = 0.15, 0.71) or in a common law relationship (RR = 0.52, 95% CI = 0.33, 0.81) were associated with a decreased risk of reinfection.[4] A case-

control study in San Francisco, US comparing risk factors between individuals with first time infection (controls) and reinfection (cases) found that cases were more likely to be black (OR = 2.96, 95% CI = 1.29, 6.77) and have a history of chlamydia (OR = 2.94, 95% CI = 1.38, 6.26) and less likely to have completed high school (OR = 0.47, 95% CI = 0.23, 0.95).[53]

Sexual behaviour factors (e.g. number of sexual partners and frequency of condom use) and medical access (e.g. number of medical visits in the past 5 years) were not found to be associated with repeat infection in a number of studies.[53,87-89] These findings highlight the importance of an individual's surrounding community (i.e., sexual networks) in the transmission of gonorrhea as a result of the observed lack of association between individual sexual behaviour/medical access and gonorrhea.

2.5.6 Risk Factor Perspectives

There is a substantial amount of epidemiological research identifying the risk factors associated with the acquisition of gonococcal infections however, the diversity of localized populations under investigation and statistical evidence is limited. Statistical evidence is required in order to understand the associated magnitude of risk.[90] In the face of highly resistant untreatable strains of *N. gonorrhoeae* coupled with the rising incidence, local analysis of surveillance data and the identification of risk factors are required in order to reduce transmission. Previous research identifying population and spatial variation in risk factors emphasizes the need to ameliorate local risk factor identification.[14] Additionally, the importance of partner characteristics and an individual's position within a sexual community highlights the importance of

investigating the role sexual networks have on the transmission of gonorrhea. Passive surveillance data gathered as a result of the Nationally Notifiable Disease (NND) list provides an opportunity of retrospectively analyzing epidemiological and sexual network-based risk factors associated with gonorrhea in Canada.

2.6 Infectious Disease Reporting in Canada and Ontario

2.6.1 National Surveillance

The NND list includes high priority infectious diseases agreed upon by the federal, provincial and territorial governments, which must be monitored and reported in Canada.[91] The NND list provides a standardized instrument for disease surveillance, which supports the health of Canadians and ensures accurate reporting of specified diseases for international infectious disease surveillance activities.[91] The Canadian government has coordinated surveillance of diseases found on the NND list since 1924.[92] Gonorrhea has remained on the NND list since 1924 and ranked 26th out of the 48 infectious diseases included in the most recent priority-setting exercise conducted in 2005.[93]

The federal government is responsible for the monitoring, coordination and collation of data reported for diseases found on the NND list by provincial and territorial public health organizations such as PHO.[91] The Public Health Agency of Canada (PHAC) summarizes the surveillance STI data gathered provincially and territorially and helps guide public health efforts and inform policy makers.[5]

2.6.2 Notifiable Disease Surveillance in Ontario

The Ontario Public Health Standards (OPHS) published by the MOHLTC under the authority of the *Health Protection and Promotion Act* (HPPA) provides guidance to the PHUs in Ontario for the collection, reporting and information transfer of reportable infectious diseases.[94] A mandatory set of variables outlined in Ontario Regulation (O. Reg.) 569 under the HPPA must be reported for each notifiable disease case.[95,96] The notifiable disease list specific to Ontario is outlined by O. Reg. 559, *Specification of Reportable Diseases*.[96] The board of health of each PHU is mandated to use the iPHIS to report all relevant information to PHO of both cases and contacts of reportable diseases.

The data is then collated and analyzed at the provincial level and used to inform testing and treatment guidelines for notifiable diseases in Ontario.[97] PHO in collaboration and consultation with a number of organizations and individuals develop the disease specific guidelines. The Guidelines for the Testing and Treatment of gonorrhea are developed by PHO in collaboration and consultation with the Ontario Multi-drug-Resistant *Neisseria gonorrhoeae* Working Group, the MOHLTC, Medical Officers of Health, the Provincial Infectious Disease Advisory Committee (PIDAC) on Communicable Diseases, PIDAC Sexually Transmitted Infections Working Group, Medical Directors of STI clinics, primary-care and specialist healthcare providers.[97]

Although reporting at the national and provincial level impacts the development of guidelines and resource allocation, the characteristics of local populations are lost in the collation of data. Despite the PHU-specific data gathered in Ontario, an in depth risk factor assessment by region is not performed. Fortunately, the reporting of diseases by each PHU in Ontario enables retrospective analysis of both individual and network-based

characteristics of local populations.[91] The reporting and resulting gonorrhea specific information provides an excellent opportunity to examine ways in which the data can be utilized more strategically at a local level. The extraordinary capacity for *N. gonorrhoeae* to develop resistance against newly introduced antimicrobial agents further highlights the importance of enhanced analysis of surveillance data.

2.7 Antimicrobial Resistance

The recurrent development of gonococcal resistance for a number of previously effective antibiotic classes highlights the global public health problem concerning gonorrhea. Consequently, enhanced efforts in the prevention and control of gonococcal transmission are required to limit the spread of resistant strains and limit the number of untreatable cases.

Antibiotics are either bactericidal or bacteriostatic drugs designed to kill or inhibit the growth of pathogenic bacteria infecting a human or animal host.[98] This is accomplished through antibiotic interactions with specific cellular target sites of the infectious bacteria. The primary outcomes associated with specific drug-target interaction are disruption of DNA, RNA, cell wall and protein synthesis and inhibition of essential metabolic pathways.[98] The interruption of the normal cellular processes inhibits effective cell development and results in cell death or the inability to grow and proliferate.[98] Antibiotics are classified based on the specific mechanisms of action achieved through drug-target interaction. The drug-target interactions are the principle behind the development of effective antibiotics.[99]

The antibiotic era began in the early 1940s following the discovery of antimicrobials and subsequent use in combating infectious diseases caused by pathogenic bacteria.[99] Shortly after the introduction of antibiotics, bacteria began to evolve by utilizing and creating resistance genes capable of evading the noxious effects of antimicrobial agents.[99] Resistance genes originate from either the intrinsic composition of the bacterial genome or through genetic mutations influenced by both environmental pressure and horizontal gene transfer.[99] Genetic mutations arise from chromosomal mutation and acquisition of genetic material from resistant strains. Resistance genes provide a defense against antibiotics through numerous mechanisms including but not limited to the production of enzymes with the ability to destroy the antimicrobial agent, prevention of the drug from binding with the specific bacterial target site and the development of a modified outer membrane which no longer contains the target surface constituents.[99]

Since the 1940s, AMR has continued to evolve, resulting in a range of severity from resistance to a single class of antibiotics to EDR strains.[100] AMR complicates both individual-case management and population-based disease control. The continued and worsening AMR is further complicated since the vulnerable bacterial target sites have been exploited by antibiotics developed to inhibit their function.[98] Therefore, the ability to create new classes of antibiotics is extremely complicated resulting in a drastic decrease in antimicrobial therapy development.[98] Following the golden era of novel antibiotic discovery between 1950 and 1970, very few classes of antibiotics have since been identified.[7] In addition to this, pharmaceutical companies have greatly decreased research and development initiatives aimed at creating new classes of antibiotics.[101] This

lack of interest can be attributed to the complexity, expense and length of time associated with novel antibiotic class development.[101] Consequently, novel therapeutic solutions to the emerging AMR involve modification and recombination of existing antibiotics.[7]

The worldwide increase in AMR to all classes of antibiotics has resulted in increased health care cost and a threat of returning to the early 20th century where non-serious infections result in complicated health outcomes.[100] Individuals suffering from antimicrobial resistant infections experience a delayed recovery due to ineffective treatment, prolonged illness and recurrent infections and consequently have a greater morbidity and mortality rate.[102]

2.7.1 Gonococcal Resistance Surveillance Systems

Gonorrhea continues to be a major global health concern due to increasing incidence, ease of transmission and the spectrum of serious health outcomes caused by gonococcal infections. The burden of this infection is further amplified due to the evolving AMR observed since the introduction of antibiotics as a treatment option for gonococcal infections.[6]

Consequently, the National *Neisseria gonorrhoeae* Surveillance Program has conducted ongoing monitoring of gonococcal resistance as part of the National Surveillance Program lead by the PHAC since 1985.[12] Canadian gonococcal resistance rates are determined through analysis of isolates submitted to the National Microbiology Laboratory (NML) from provincial and territorial public health officials.[50] Isolates are submitted to the NML when resistance to a minimum of one antibiotic is identified by provincial laboratories or in situations where the province/territory is unable to perform

susceptibility testing.[50] The Canadian national enhanced surveillance protocol integrates laboratory-based monitoring of antimicrobial resistant *N. gonorrhoeae* with reported epidemiological data.[50] The objective of the enhanced surveillance protocol is to identify risk factors associated with the development of resistance.[97]

The understanding of gonococcal infections in Canada has been strengthened through national surveillance however, limitations with the surveillance system are apparent. The inclusion of isolates with resistance to at least one antibiotic or from provinces/territories without the capacity to perform susceptibility testing results in a non-representative sample.[12] Furthermore, the submission of provincial/territorial isolates is voluntary and is not standardized across the country, which may further contribute to a non-representative sample.[103]

Analysis of resistance at the provincial/territorial level improves the understanding of geographic resistance trends. In Ontario, gonorrhea specific resistance data includes isolates which were submitted to one of the 11 PHO laboratories across Ontario. Recommendations which differ from the Canadian guidelines are guided by Ontario based evidence.[97] Although, resistance data is analyzed by PHO with the objective of strengthening the provincial testing and treatment recommendations a number of limitations are apparent.[97] Firstly, resistance data from private laboratories are not submitted to PHO, which contributes to a non-representative sample. Additionally, risk factor data is not combined with resistance data at the provincial level. Therefore, important risk factors associated with resistant gonorrhea are likely lost in the collation of data across Ontario. Previously identified geographic and population specific (e.g. MSM, sex-trade workers) variation in resistance trends highlights the need to enhance analysis

conducted at the provincial and local level in order to utilize available data and identify local risk factors contributing to gonococcal resistance.[6,14]

In the US, resistance and susceptibility data are primarily gathered and analyzed through a CDC sponsored program known as the GISP. The national sentinel surveillance system was developed in 1986 due to emerging gonococcal resistance.[6] Approximately 6000 male urethral gonococcal isolates are obtained annually from 25 to 30 STI clinics in the US.[104] Although the GISP has improved AMR understanding in the US, a noteworthy limitation is the lack of generalizability of the susceptibility/resistance findings. The isolates collected are not representative of the total population since the sample represents 4% of male urethral isolates and does not include females.[6] Additionally, a large proportion (70%) of gonorrhea cases are diagnosed in clinical settings other than the publicly funded STI clinics included in the GISP sample.[105,106] The oversampling of the West Coast and aggregation of isolates from distant geographic areas also inhibits the analysis of geographic variation in resistance.[6,105]

The information gathered through the aforementioned surveillance systems has provided the most up to date information regarding gonococcal resistance and epidemiological trends in North America.[5,104] The CGSTI and CDC recommendations for treatment of gonorrhea are based on the findings of the aforementioned surveillance systems.[5,52] Although the surveillance systems provide the rationale for national and provincial treatment recommendations, the limitations highlight the importance of conducting local surveillance.[6] Local surveillance can help to promote rapid knowledge translation of the evidence required to guide timely treatment recommendations and identify region-specific risk factors for resistant strains of *N. gonorrhoeae*. The lack of

representation of specific geographical locations and populations during national surveillance further supports the need to implement effective local surveillance programs. With the emerging threat of untreatable gonorrhea, it is especially important to act rapidly when faced with highly resistant gonococcal strains in order to prolong the effectiveness of the currently recommended antibiotics. Rapid development of resistance against initially effective antimicrobial therapies observed through surveillance systems influences the cyclical act of introducing, analysing and replacing first line antibiotic treatment recommendations.[104]

2.7.2 Treatment Guidelines

The extraordinary capacity of AMR exhibited by *N. gonorrhoeae* necessitates the implementation and adherence to stringent treatment guidelines. The WHO and CDC recommend a change in treatment when the prevalence of resistance exceeds 5% in a given location.[107] Currently, national surveillance systems guide the nation-wide recommendations for treatment of gonorrhea based on resistance rates. Enhanced local surveillance however, is required to ascertain whether population and geographic specific resistance rates follow similar national trends or whether the specific population would benefit from altered treatment recommendations.[6] Interpretive criteria have been developed to determine the susceptibility of *N. gonorrhoeae* for antimicrobial agents in order to accurately define the degree of resistance exhibited by gonococcal strains.[108]

The Clinical Laboratory Standards Institute (CLSI) is an international, not for profit, consensus driven organization developed to provide standards and guidelines in health care testing.[108] The CLSI defines minimum inhibitory concentration (MIC)

breakpoints used to identify and classify AMR.[108] MICs are defined as the lowest concentration of an antibiotic required to inhibit visible bacterial growth.[108] Interpretive criteria for MIC breakpoints are defined as susceptible, intermediate and resistant.[108] An isolate is defined as susceptible when the serum antimicrobial concentration achievable with the recommended treatment is able to successfully inhibit bacterial growth *in vitro*.[108] Intermediate antimicrobial agent MICs are usually attainable however, isolates are less responsive to the antibiotic. The resistant category identifies isolates, which are not inhibited by the antimicrobial concentration achievable with the recommended treatment dosage. Furthermore, increased dosages of the antibiotic for which resistance has been identified have not been determined to be effective through clinical research.[108]

Treatment recommendations for gonorrhea have continuously changed since the introduction of antimicrobial treatment in the 1930s.[109] The change in treatment has been guided by the determination of *N. gonorrhoeae* specific MIC breakpoints in order to identify resistance rates and determine the effectiveness of the current treatment recommendation.

2.7.3 Treatment History of Gonococcal Infections

The introduction of sulfonamides as a treatment option for gonococcal infections in the late 1930s revolutionized therapy.[109] The specificity of the antimicrobial, improved patient comfort and timeliness of the therapeutic process created great optimism for the care of patients suffering from gonorrhea.[109] Nonetheless, sulfonamides never achieved 100% success and resistance to treatment was rapidly observed.[109] In 1943, penicillin was shown to effectively treat gonorrhea and demonstrated success in the treatment of

sulfonamide resistant gonococcal strains.[110] With poor sulfonamide success and the advent of penicillin treatment, penicillin became the antibiotic of choice when treating gonorrhea.[109] In 1945, sulfonamides were no longer recommended for the treatment of gonorrhea.[6] Penicillin remained the recommended therapy for over 40 years with tetracycline introduced as an effective alternative in patients with penicillin sensitivity.[6,111] Resistance to penicillin steadily increased between 1940 and 1980, with resistant isolates documented as early as 1946. Increased penicillin dosage was used to combat the resistance against penicillin nevertheless, widespread penicillin and tetracycline resistance rendered the antibiotics ineffective in 1989.[6,8]

Oral fluoroquinolones such as ciprofloxacin and the oral cephalosporin cefixime were introduced as the recommended treatment in 1990s due to high therapeutic effectiveness, safety and convenience of a single-dose oral treatment regimen.[6] Resistance to fluoroquinolones steadily increased between 1990 and 2000.[6] Populations first exhibiting significant resistance were identified in Asia, the Pacific Islands including Hawaii, and California.[112] Consequently, fluoroquinolone treatment was discontinued in these geographic regions.[112] Continual increases in resistance observed in MSM in various geographic regions led to the discontinuation of fluoroquinolones as a recommended therapy in the MSM population.[6] In 2007, resistance to fluoroquinolones became widespread and the CDC no longer recommended fluoroquinolones as first-line therapy for gonococcal infections.[104] Similar fluoroquinolone resistance trends have been observed in Canada with AMR for fluoroquinolones increasing from 0.3% in 1994 to 25.9% in 2009.[12] Based on the national trends and CDC recommendations, the CGSTI no longer included fluoroquinolones as of 2008.[12] Decreased susceptibility for cefixime has

also been observed in various populations and geographic locations (for a detailed discussion see section 2.7.5 First-Line Antibiotic Resistance Trends).

2.7.4 Current Treatment Recommendations

Presently, only one class of antibiotics, the Extended Spectrum Cephalosporins (ESC) are recommended as first-line treatment of gonococcal infections.[113] The CGSTI, CDC and British Association for Sexual Health and HIV currently recommend dual therapy of an intramuscular injection of the ESC ceftriaxone combined with oral azithromycin (preferred) or doxycycline (part of the tetracycline antibiotic class) as first-line therapy for gonococcal infections.[97] Azithromycin is the preferred adjuvant treatment due to the convenience of a single-dose regimen and observed prevalence of tetracycline resistant *N. gonorrhoeae*.[97,114] In Ontario, the recommended first-line treatment for gonorrhea is an intramuscular injection (250 mg) of ceftriaxone combined with oral (1g) azithromycin.[97]

Intramuscular injections of ceftriaxone are currently the most effective in treating genital and non-genital site infections.[115] Intramuscular ceftriaxone sustains high serum bactericidal levels capable of effectively treating infection.[113] Oral cefixime, although more conveniently administered as a single oral dose, does not sustain the same bactericidal levels and is less effective in the treatment of gonorrhea, specifically pharyngeal infections.[113] An oral ESC cefixime is recommended when ceftriaxone is unavailable, the patient refuses intramuscular treatment or due to a contraindication.[115,116] Bleeding diathesis (e.g. haemophilia, individual on blood thinners) is the main contraindication for intramuscular injections. Additionally, the US Food and Drug Administration recommend that ceftriaxone and calcium-containing products are not

administered within five days of one another for patients younger than 10 weeks.[117] Alternative effective injectable cephalosporins include ceftrizoxime, cefoxitin and cefotaxime.[113] Ceftriaxone however, is the most effective in treating gonococcal infections at all targeted anatomical sites.[113]

Azithromycin or doxycycline are combined with ceftriaxone with the purpose of targeting alternative molecular sites on the gonococcus, which is hypothesized to delay the emergence and spread of AMR.[97] Additionally, both adjuvant therapies are capable of treating the common coinfection chlamydia.[115]Azithromycin, a type of antibiotic macrolide, is not recommended as a monotherapy due to the suspected ease in which *N. gonorrhoeae* can develop resistance against macrolides.[118] Nevertheless, patients with an allergy to cephalosporins are treated with 2g of oral azithromycin however, this therapy should be highly restricted to only these patients.[115] A test for cure is strongly advised in patients who receive this treatment due to the increased probability of resistance.[118] Culture within one week is the recommended test for cure, when unavailable a nucleic acid amplification test (NAAT) should be performed three to four weeks following treatment.[118] When NAATs are used as a test of cure, the delay in follow up is implemented with the objective of reducing false positives. A NAAT may yield a false positive due to the detection of DNA in dead bacteria.[97] Despite the current recommendations, resistance to both ESCs and azithromycin are on the rise.[115]

2.7.5 First-line Antibiotic Resistance Trends

2.7.5.1 MIC Breakpoints for ESCs

The CLSI has not yet defined the interpretive criteria for either cefixime or ceftriaxone

resistance.[108] For pathogens whose resistance to antimicrobials remains rare, criteria for susceptibility are solely defined.[108] Enhanced data regarding the MICs for ESCs in treatment failure cases are required in order to establish intermediate and resistance MIC breakpoints.[9] Susceptibility for both cefixime and cephalosporins are defined as a MIC of ≤0.25 μg/mL.[108] The CLSI has created a threshold for decreased susceptibility for cefixime and ceftriaxone as MICs of ≥0.5 μg/mL.[104]

2.7.5.2 Public Health Agency of Canada

In Canada, both cefixime and ceftriaxone MICs have progressively increased between 2001 and 2009. Gradual increases in MICs are reported to occur prior to the development of resistance to a particular antibiotic.[12] Between 2001 and 2009 the modal MIC for ceftriaxone increased from 0.016 μg/mL to 0.063 μg/mL. Increases in MICs for cefixime were also observed and three modal MICs of 0.016 μg/mL, 0.032 μg/mL and 0.125 μg/mL were reported.[12] Fifty gonococcal isolates were identified to have MICs of 0.125 μg/mL and 0.25 μg/mL for ceftriaxone and cefixime respectively, classified as elevated MICs according to US based standards developed through the GISP analysis (see section 2.7.5.4 Gonococcal Isolate Surveillance Program).[12] Reduced susceptibility to both ESCs, defined by exceeding the susceptibility breakpoint of 0.25 μg/mL, was observed in 208 isolates and three isolates were found to have decreased susceptibility to cefixime (MIC ≥0.5 μg/mL). A greater number of isolates demonstrated a decrease in susceptibility for cefixime compared with ceftriaxone.[12]

Increases in resistance for azithromycin have been observed. The modal MICs have increased from 0.25 μg/mL to 0.5 μg/mL between 2001 to 2009.[12] In 2009, greater

than half of the isolates demonstrated MICs of 0.05 μg/mL, which is rapidly approaching the resistance breakpoint classified by the CLSI.[12]

2.7.5.3 Public Health Ontario

In Ontario, cefixime is no longer recommended as first-line therapy due to decreased susceptibility and treatment failures.[97] The resistance data in the US reflects trends observed in Canada between 2000 and 2009. Approximately 10% of all infections in Ontario between July 2010 and October 2012 were caused by gonococcal strains with increased resistance to cefixime and nine treatment failures have been documented.[97] PHO based this change on the WHO and CDC recommendation of discontinuing an antibiotic with a 5% or greater prevalence of resistance.[97]

2.7.5.4 Gonococcal Isolate Surveillance Program

The most recent extensive AMR trends in the US are based on the isolates collected and analyzed by the GISP between 2000 and 2011.[104] A limited number of isolates included in the GISP analysis resulted in MICs above the decreased susceptibility threshold (MICs $\geq$0.5 μg/mL) therefore, a measure of elevated MICs for both antibiotics was developed to identify less evident trends in resistance.[104] Elevated MICs for cefixime and ceftriaxone were defined as $\geq$0.25 μg/mL and $\geq$0.125 μg/mL respectively.[104] Surveillance data from the GISP has identified greater resistance for cefixime when compared with cephalosporin.[104] Between 2000 and 2011 the rate of elevated MICs in the US has increased from 0.2% to 1.4% for cefixime and 0.1% to 0.3% for ceftriaxone.[104] Increases in elevated MICs for both cefixime and ceftriaxone were considered significant.[104]

During the same time period, decreased susceptibility to cefixime increased from 0.02% to 0.11%, a statistically significant increase.[104] No isolates were found to have decreased susceptibility to ceftriaxone between 2000 and 2011.[104]

A decrease in susceptibility for azithromycin was initially observed in Hawaii in 1999.[118] Since then, decreased susceptibility is progressively increasing in various states in the US. The first highly azithromycin resistant isolate was reported in Hawaii.[118]

2.7.5.5 Global Gonococcal Resistance

Gonococcal strains with reduced susceptibility for ESCs is hypothesized to have originated in Japan and has spread internationally to Southeast Asia, China, Hong Kong, Taiwan, US, Canada, Australia, South America, Russia and 17 countries in the European.[9,104,119] Poor susceptibility has resulted in treatment failures in a number of the aforementioned geographical locations.[9] Commonly occurring treatment failures in Japan has resulted in the exclusion of ESCs as first-line treatment in 2006.[9] Cefixime treatment failures have also been identified in Norway, France, Austria and the United Kingdom.[9] Ceftriaxone treatment failures of pharyngeal infections have been reported in Australia, Slovenia and Sweden.[9]

In recent years, EDR strains of *N. gonorrhoeae* including resistance to both ceftriaxone and cefixime have been identified in Japan, France and Spain.[8,9] The original EDR strain identified in Japan was highly resistant to both ceftriaxone and cefixime and the majority of the additional 28 antibiotics tested.[120] EDR strains of gonorrhea are defined as those resistant to one or more antibiotics recommended globally as first-line treatment (ceftriaxone and cefixime) and three or more antibiotics less frequently used

due to previously established resistance.[121] Increased international transmission of EDR gonococcal strains poses a serious global health threat due to the reduced ability to effectively treat these infections.[8] Although gonococcal AMR to the last remaining first-line treatment has steadily increased globally over the last decade, ESCs remain effective in treating the majority of gonococcal strains.[104]

2.7.6 Risk Factors of Resistant Gonococcal Strains

Limited research has identified risk factors associated with resistant gonococcal strains however, recent analysis of gonococcal isolates from 21 countries submitted to the European Gonococcal Antimicrobial Surveillance Programme has revealed patient variables associated with resistance to cefixime, ciprofloxacin (part of the fluoroquinolone class of antibiotics) and azithromycin.[122] The isolates with resistance to the three antibiotics were significantly associated with heterosexual males, individuals 25 years or older and a non-concurrent chlamydial infection.[122] The ability to accurately identify risk factors associated with resistant gonorrhea requires improvements in national, provincial and local surveillance in order to conduct an accurate and representative analysis. The identification of risk factors associated with resistant gonorrhea and development of prevention strategies is required due to the limited therapeutic options available to treat gonorrhea. Treatment alternatives have been theorized however, limited evidence of effectiveness and safety currently exist.

2.7.7 Alternative Treatments

Alternative solutions to the current recommended therapy include increased doses of

ESCs, dual therapy and potential monotherapy with gentinomycin or spectinomycin.[8] In Canada, spectinomycin is widely available, however must be accessed through Health Canada's Special Access Program and can only be used for specific indications.[50] Spectinomycin is currently used to treat gonorrhea when first-line medications have failed, are unsuitable (when a patient has a cephalosporin allergy) or unavailable.[50] The use of spectinomycin as an alternative treatment is a risk since, rapid resistance emerged following its use as first-line therapy for the US military in South Korea in the 1980s.[8] Additionally, spectinomycin is unable to treat pharyngeal gonorrhea.[8] Although gentinomycin is currently used in Malawi as first-line therapy, gonococci susceptibility, dose requirements and ability to treat genital and extragenital infections remain unknown.[8] Additionally, the observed cure rate is 91%, which is below the 95% effectiveness recommended by the CDC and WHO.[8,107] Lastly, the effectiveness of an increase in ESCs dose and dual therapy with other antibiotics remains unknown.[8]

The complicated and highly adaptable nature of *N. gonorrhoeae* has prevented the development of a vaccine for gonorrhea.[8] Vaccine development is further complicated by the local, non-persistent immune response, which provides little to no protection against a subsequent infection with an identical strain of gonorrhea.[8]

2.7.8 Implications of Gonococcal Resistance

The increase in AMR results in serious implications for the treatment of gonorrhea leading to complicated health outcomes. The inability to treat infection increases the likelihood of PID in women, infertility in both men and women and neonatal conjunctivitis leading to blindness.[3] In the most severe cases, gonorrhea can cause death

through DGI.[10] The inability to treat gonorrhea also increases the period of infectiousness leading to an increase in transmission of both gonococcal infections and HIV.[4] With the cost of treating patients with gonorrhea and associated health sequelae estimated to range between $30 to $74 million dollars CAD in 1991, healthcare cost as a result of resistance and increased transmission is predicted to greatly increase.[4] The recent switch to dual therapy combining intramuscular ceftriaxone injections and azithromycin provides an example of an increase in the cost of treatment and reduced ease of administration which are expected to continue with antimicrobial resistant *N. gonorrhoeae*.[3] Additionally, long-term consequences will continue to rise resulting in an increase in individual expenditure as a result of health sequelae, inability to maintain daily responsibilities and increased drug cost.[3]

The history of AMR and emerging resistance foreshadows the widespread resistance expected to develop with ESC therapy. Presently, no alternative single antibiotic or combination therapy exists as a clinically tested substitute to the current treatment recommendations.[104] Resistance to ESCs in combination with a number of additional antibiotic classes including sulfonamides, penicillins, tetracyclines, quinolones and macrolides has classified *N. gonorrhoeae* as an EDR pathogen.[119] The development of gonococcal strains with resistance to both ESCs and azithromycin poses a serious threat and would significantly limit effective therapeutic options.[118] With the standstill in novel antimicrobial therapy development and lack of vaccine, prevention/control strategies are vital in limiting transmission and prolonging the effectiveness of current first-line treatment recommendations. Specific to AMR, local surveillance is a crucial strategy in rapid detection of treatment failures due to decreased antibiotic susceptibility.

Effective identification of these cases will promote effective local treatment, limit the transmission of resistant gonococcal strains and improve patient health outcomes. In order to effectively monitor the development of gonorrhea cases, both resistant and non-resistant, accurate and timely diagnosis is required. With the introduction of NAATs as a rapid alternative to the conventional bacterial culture, the benefits and risks of the increasingly popular diagnostic method requires attention.

2.8 Diagnosis

The most commonly used diagnostic tests for gonorrhea include bacterial culture and NAATS.[118] Until the late 1980s gram staining and bacterial culture were the two available methods for the diagnosis of gonorrhea.[123] Gram staining has similar sensitivity in male urethritis as bacterial culture, however, is relatively insensitive in women and for specimens taken at extragenital sites.[123] Therefore, bacterial culture became and has since remained the gold standard for definitive diagnosis of gonorrhea.[123] Benefits of using bacterial culture include low cost, the ability to diagnose infections at various anatomical sites and isolation of a viable organism required for antibiotic susceptibility testing.[123] In order to perform a culture, invasive specimen collection is required and must be transported to a laboratory with the capacity to perform cultures under stringent conditions to maintain the viability of the organism.[123]

NAATs were introduced in the early 1990s and presented an alternative, non-invasive diagnostic method with greater sensitivity than bacterial culture.[123,124] Optimal specimens for NAATs include urine samples in males and females, in addition to cervical swabs in females.[125] Higher sensitivity results in a greater number of identified cases and

is therefore beneficial in the screening of symptomatic and asymptomatic individuals.[123] NAATs are able to diagnose gonococcal infection earlier than bacterial culture since NAATs are able to detect small amounts of DNA or RNA.[50] The majority (75% of current tests) of gonorrhea testing is now performed using NAATs due to the aforementioned benefits.[10,118] Nevertheless, NAATs have a decreased specificity in detecting pharyngeal and rectal infections and are unable to detect AMR since a viable organism is not obtained.[126] The shift toward the use of NAATs has caused a decrease in the surveillance of antimicrobial resistant *N. gonorrhoeae*, which negatively impacts the ability to rapidly treat and prevent the spread of these bacterial strains.[118]

The PHAC strongly recommends culture as the primary mode of diagnosis, however, NAATs can be used when storage and transport of the viable specimen is not ideal for culture or when patients refuse invasive specimen collection.[127] In the case of a treatment failure, culture tests are solely recommended in order to test for antibiotic susceptibility.[50] In Ontario, PHO recommends symptomatic males undergo either a urethral culture or urine NAAT while females should be tested using a cervical culture swab or cervical NAAT.[97] Asymptomatic individuals suspected to have a gonococcal infection should undergo screening using a urine NAAT for males and cervical swab culture or cervical NAAT for females.[97]

Maintaining bacterial culture in both Canada and around the world is required in order to maintain vigilant surveillance of the development of EDR gonococcal strains. It has been hypothesized that highly resistant strains are likely to emerge from countries with limited surveillance systems therefore, countries with the capacity to maintain

susceptibility testing will play an integral role in preventing the global spread of infection.[8]

2.9 Network Analysis

Despite the identification of risk factors associated with gonorrhea through epidemiological and national surveillance efforts, the incidence of gonorrhea continues to rise. In attempts to overcome the limitations currently faced by the national surveillance system, novel, localized methods of analyzing surveillance data are essential in reducing transmission and prolonging the effectiveness of ESCs.

Interestingly, NA has been used in the area of STIs to better understand the role sexual relationship patterns of a given population have on STI transmission during endemic, epidemic and outbreak settings. An improved understanding of transmission and identification of network-based risk factors is likely to enhance the ability to effectively interrupt the transmission of STIs through prevention/control strategies.

2.10 Rationale for Sexual Network Analysis

Epidemiological research has identified single clusters of individuals (i.e., core groups) as the source of gonorrhea persistence and spread in a given population.[53,55,56,88,89,128] The critical concept in disease epidemiology known as the basic reproductive number (R_0) explains the importance of core groups in the transmission of STIs.[59] The R_0 is defined as the average number of secondary infections caused by an infected individual in a susceptible population and is a function of three components including the transmissibility of disease, the contact rate between infected and susceptible individuals

and the duration of infectivity.[129] A R_0 less than one identifies a lack of transmission leading to the elimination of the infection in a given population. When the R_0 is equal to one the disease is in an endemic state whereas a number greater than one identifies an increase in transmission leading to an epidemic.[129] It has been hypothesized that in the general population an insufficient amount of sexual partner exchange occurs for gonorrhea to be successfully maintained. Therefore, the core groups with a greater amount of partner exchange enable the transmission and spread of gonorrhea in a population.[59,130]

Previously, core groups were defined as individuals with a subset of factors classifying them at an increased risk of infection whereas recent research has identified sexual networks as the source of core groups.[55] Although multiple investigations have utilized independent risk factors (e.g. race, SES status and reinfection rates) as the determinants of core group membership, limited research has identified the characteristics of gonococcal-networks responsible for core group formation and the maintenance of infection.[55,56,88,89,128] The sexual network approach, derived from social NA, focuses on the sexual linkages between network members while incorporating individual risk factors to better understand infection transmission within the network. Specific network characteristics have been identified as having a greater significance in the risk of gonorrhea acquisition compared with individual attributes therefore, the specific sexual partnership structures within a sexual network of given populations require further investigation. [32,51,54] A glossary of terms for terminology specific to NA can be found in Appendix D.

2.11 Development of Social Network Analysis

Network theory employs sophisticated mathematical models developed to study a specific type of graph representing the relations between discrete entities.[15] Both social[16,17] and sexual[18] NA, derived from network theory, are used to better understand the transmission of STIs.[19] Sexual NA was developed based on the foundations of social NA, which will be discussed in detail to provide a comprehensive understanding of network concepts.

Social NA is an interdisciplinary research field focused on analyzing the relational structure of a given population.[20] Social NA employs network theory in order to quantitatively analyze social relationships and their implications.[131,132] Specifically, the objective of social NA is to determine how relationships influence human behaviour and characteristics.[133] Social NA evolved from the concept of sociometry, the measurement of interpersonal relations among small groups, introduced in the early-1930s.[20] Diagrammatic representations of social linkages in small groups known as sociograms, were the first analytical tool developed to better visualize and understand relationships and their impact on group characteristics.[20] Sociograms are a type of graph known as a network, composed of points, referred to as nodes, and edges representing specific linkages between the nodes.[131] The nodes in a social network represent individuals and social actors such as groups and organizations, connected with other nodes through social relationships, represented by edges between the nodes.[20] The introduction of the sociogram was met with great enthusiasm and led the development of various analytical techniques designed to quantitatively analyze and measure the visual representations of social relationships.[20]

Theoretical, conceptual and methodological advances made in many fields such as sociology, statistics, computer science and mathematics (specifically graph theory), strengthened the foundation of sociometry research between 1950 and 1970.[134] Matrix algebra was introduced as a method of representing social relationships and facilitated the development of advanced sociograms.[135] The application of the evolving NA with complex populations further influenced the development of sophisticated methods designed to better analyze and understand social linkages and their impact on a population.[20]

2.12 Modern Perspective

Social NA now incorporates the graphing, analyzing and measuring a system of complex social relations, which is then used to describe the relationship structure of a given population. Patterns and regularities of social relationships are quantitatively analyzed through network measures.[17,20] The relationship structures of a network are measured from three distinct levels including the individual micro-level, the network structure meso-level and the overall network structure macro-level.

The individual level is focused on the actor's position within the network. Network measures of centrality are used to determine whether an individual maintains an influential role within a larger network (see section 3.4.2.2 Individual Network Centrality). Network structure measures focus on subgraphs within a larger network. A subgraph describes a group of individuals who are connected directly or indirectly with one another.[136] More specifically, subgraphs involving two or three individuals are referred to as dyads and triads, respectively, and a subgraph with greater than three

individuals is termed a component. To ensure consistency, the term component will be used regardless of size and when needed the number of individuals involved in the component will be stated. Measures of interconnectivity and centralization are two examples of network structure measures applied to components. The interconnectivity of a component determines the magnitude of transmissibility within a component.[136,137] Centralization identifies the degree to which a component is centralized around a single individual (see section 3.4.2.1 Network Structure).[136] The overall network-structure level provides mean scores of the individual and network structure level measures. Therefore, the influence of a society or community on individual behaviour or characteristics can be determined through the analysis of the social relationships between social entities.[133]

The measurement and analysis of the relational structure of a population through social NA combines four important concepts: 1.) Social NA is grounded on the assumption that links between social actors are important, 2.) Social NA is established through the collection and analysis of data concerning social actors and their relations, 3.) Graphic representations of social relations are integral in displaying and understanding relationship patterns and 4.) Regularities in relationships are described with mathematical models.[138] Additionally, actors are considered interdependent, linkages between actors are viewed as channels of transfer and flow of resources, and the network structure provides both opportunities and constraints for the individual actors.[20] NA is now utilized in public health and epidemiological research.[135,139]

2.13 Public Health Focus

The identification and analysis of relationship patterns is recognized as an important element in understanding health and disease from a population perspective and has been employed in epidemiological research which informs public health practice.[133] Networks play a role in the causes, experiences and consequences of health problems including both infectious and chronic conditions.[133] Individual detection of disease, medical knowledge acquisition, barriers to care, treatment and caregiving for example, are strongly influenced by an actor's position within a larger social network.[133] Public health concerns can be approached through the analysis of social, organization and disease transmission networks of specific populations.[134] Previous research has revealed a significant impact of social and sexual networks on the transmission of infectious diseases.[133] The impact of sexual networks on STI transmission has become an important focus in epidemiological research and is the focus of this thesis.

2.14 The Epidemiology of Infectious Diseases

The epidemiology of infectious diseases, which informs public health initiatives through evidence-based research, is centered on identifying the frequency of infectious disease cases over time and individual risk factors in order to develop an understanding of disease trends in a given population.[134] Additionally, risk factors for infection are commonly determined by comparing attributes between infected and non-infected individuals.[140] Analysis focused on individual characteristics and the epidemiologic curve however, fails to capture the complexity of relationships between individuals in a population, which drive the transmission of infection.[134,141] An individual's risk of

infection is based on their sexual partner's risk/behaviour and the wider sexual network to which they belong.[140] Consequently, networks play a vital role in understanding the epidemiology of STIs by revealing the relationship structures of a given population.[134] Therefore, sexual NA is believed to support the study of infectious disease transmission and build on the information gathered through the traditional epidemiological approach.

The importance of incorporating NA in epidemiological research is demonstrated through the evolution of core group classification. As previously mentioned, the identification of core groups has been a part of the conceptual framework of epidemiological STI transmission research for several decades.[142] The subset of the population defined as the core group includes a group of individuals with high rates of STIs and is targeted when developing prevention/control strategies. The core group concept however, was previously focused on the identification of individual attributes indicating membership in a high-risk population. More recently, the core group concept has been perceived as a sexual network incorporating the importance of the relationships between high-risk populations.[142] Interventions focused on individual cases rather than a comprehensive understanding of the entire sexual network limits the success of prevention/control strategies.[143] Understanding both the risk factors and determinants of sexual networks has improved the ability to develop successful prevention/control strategies and identify a greater number of individuals at risk.[143]

2.15 Network Analysis and the Study of Infectious Diseases

NA has been employed to study the transmission of a number of STIs including HIV/AIDS, syphilis, chlamydia and gonorrhea.[18] Previous research has demonstrated an

improved understanding of STI transmission through the visualization and analysis of sexual networks.[19] NA greatly enhances epidemiological research of disease transmission by generating unique data for diseases of unknown etiology, identifying network-based risk factors and informing prevention/control strategies.[16] The benefits and concepts of NA will be described followed by a gonorrhea-specific overview of previous NA research.

2.15.1 Diseases of Unknown Etiology

Following the presentation of HIV/AIDS in the US in 1981, Auerbach *et al*. created a sexual network conceptualizing the spread of the unknown pathogen.[144] The sexual network included 19 AIDs patients and 21 identified sexual partners who acquired AIDs in 10 cities in the US.[144] The CDC had previously found that the risk factors for disease acquisition, namely increased sexual partners, membership in MSM communities, sex with men belonging to high risk AIDS groups and intravenous drug use, were comparable to other infectious disease risk factors.[144] Nonetheless, the nature of the pathogen remained unknown and a NA approach was utilized in order to reveal the risk-potential linkages leading to HIV/AIDS transmission.[16]

Following the mapping of the sexual network, Klovdahl analyzed the personal-contact, temporality and non-randomness of the sexual linkages in order to support or challenge the infectious disease hypothesis for the newly introduced disease.[16] The results suggested that sexual contact was a significant contributor in disease transmission, exposure to an infected individual generally occurred prior to infection and that the pattern of sexual linkages in the network diagram were not considered random.[16] The use

of a network probability model demonstrated that the structure of linkages between infected individuals was not due to chance and resembled infectious disease transmission trends.[16] The success of the initial HIV/AIDS NA was two-fold. Firstly, it identified the usefulness of NA in supporting traditional epidemiological research in the determination of the infectious nature of a disease with an unknown etiology.[16,134,144] The successful identification of sexual linkages leading to HIV/AIDS transmission also influenced the diffusion of NA in disease transmission research of a variety of STIs.

From the advent of NA in disease transmission research, the capabilities and application have greatly evolved. The innovative potential of NA was recently demonstrated by Bogich and colleagues who developed a network model designed to identify the pathogens responsible for disease outbreaks of unknown origin.[145] The newly designed model was used to determine the causes of encephalitis outbreaks, a commonly occurring infectious disease caused by multiple pathogens, in South Asia.[145] In this network, the individual nodes represented specific outbreaks and the linkages between the nodes represented similarities in symptoms and properties of disease outbreaks. A library of known potential pathogens was built including specific symptoms and properties of encephalitis outbreaks caused by each known pathogen.[145] These data were used to identify similarities of outbreak symptoms between the known and unknown causes of encephalitis outbreaks through NA. The pilot study demonstrated great success in accurately identifying the cause of a significant proportion of the unknown encephalitis outbreaks and highlights the extraordinary capacities of NA. The ability to rapidly and inexpensively assess outbreaks would lead to improved and timely disease treatment, specifically, in resource poor areas.[145]

2.15.2 Network-Based Risk Factors

Over the past 20 years, NA research has identified network-based risk factors as key determinants of disease transmission.[24,63,86] Both network structure and individual level network based-risk factors have been identified. The distinction between networks with the capacity to easily transmit infections compared with lower risk networks improves the understanding of STI transmission in a given population. Furthermore, individual network measures identify network positions with a greater risk of transmitting and acquiring infection.

2.15.2.1 Network Structure

Network structure measures include the size, topology, interconnectivity and centralization of a component.[136] In order to visualize and quantitatively analyze the sexual network structure of a defined population, sexually active individuals and their named sexual partners are identified. The data is then translated into an adjacency matrix, which is used to graph the components within a population. The results include a number of components, which are initially classified based on their size. Network components within a defined population vary greatly in size. As previously stated, the term component will be used regardless of size and when needed the number of individuals involved in the component will be stated. Components can then be classified by shape (network topology) and network structure measures such as interconnectivity and centralization can be applied. Figure 1 depicts variation in component size and shape. The structure to the right of the single asterisk is a component with five individuals, which is

defined by a linear shape whereas the structure to the right of the double asterisk, also including five individuals, represents a radial structure.[24]

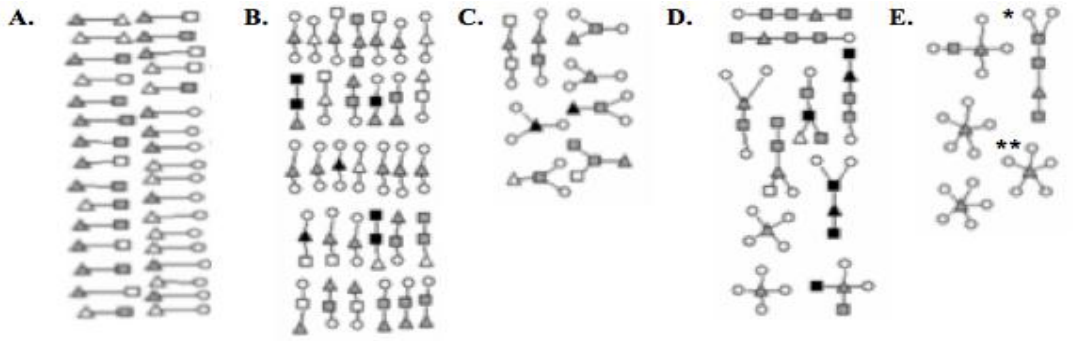

Figure 2.1. Network Components of Various Sizes. The shapes represent individuals and the lines represent sexual relationships. The colours represent study participants who were infected with either gonorrhea or chlamydia (black), non-infected individuals (grey) and individuals who were not tested (white). Components are defined by the number of nodes included: A. Dyads, B. Triads, C. Component *n*=4, D. Component *n*=5, E. Component *n*=6. The structure to the right of the single asterisk (*) represents a linear structure while the structure to the right of the double asterisk (**) represents a radial structure. Adapted from Fichtenberg and colleagues.[24]

Previous research has identified an enhanced understanding of STI transmission through the analysis of network structure. Firstly, correctly identifying the phase of an infectious disease in a population is an important feature in determining the type of prevention/control strategies required and severity of disease status.[142] Sexual network topology has previously been used to determine whether the observed components are indicative of an endemic, epidemic or outbreak setting. Comparison between traditional STI trend analysis and the sexual network structure approach has primarily lead to uniform conclusions of infection phase although opposing findings have been reported. Potterat *et al.* compared STI transmission phase conclusions using traditional surveillance data and a sexual NA in Colorado Springs between 1996 and 1999.[146] The results of the sexual NA suggested the area was experiencing endemic levels of chlamydia and

identified that the conclusion of epidemicity drawn through surveillance data was inaccurate.[146] The analysis of the shape of sexual components through NA revealed the accurate disease phase, which was later confirmed using conventional methods, in a more timely manner.[146] The lack of radial and cyclical structures (i.e., components where each individual is directly connected to every other individual included in the component) and presence of linear components were network characteristics indicative of an endemic infection phase.[146]

In addition to component size and topology analysis, measures of interconnectivity and centralization support the understanding of the magnitude of STI transmission experienced in a sexual network. A highly interconnected component for example, is indicative of high transmission rates compared with smaller, less interconnected networks.[134,147] A component with high centralization quantitatively represents a radial structure, which is centralized around a single node or group of nodes.[136] The association between highly centralized components and STI risk varies depending on the specific pathogen under investigation.[14]

2.15.2.2 Individual Network-Based Risk Factors

Individual risk factors established through epidemiological research identify individual exposures responsible for an increased risk of acquiring infection whereas individual network-based risk factors are concerned with characteristics of an individual as a result of their sexual partnerships. Therefore, the sexual network in which the individual is a member influences their risk of acquiring a STI. Network-based risk factors became a focus of STI research following the acknowledgement of the importance partner characteristics have on the transmission of STIs. Mathematical models together with

empirical research have demonstrated that specific individual network characteristics including partner mixing, bridges, concurrency and network position affect the severity and risk of STI transmission for both the individual and the larger sexual network.[22,24,147,148]

Partner mixing is focused on the differences of demographic variables and risk factors such as age and number of sexual partners between sexual partners.[22] Assortative mixing, which is most common in sexual networks, occurs when individuals with similar attributes engage in sexual activity with other like individuals.[22,32] Disassortative mixing involves sexual contact between individuals with differing risk attributes.[22,32] There is a significant increase in the risk of infection for both the population and individual as the proportion of disassortative mixing increases in a given sexual network.[22] The characteristics of partner mixing which are currently emphasized in the literature as key determinants in STI transmission include geographic location, race/ethnicity, number of sexual partners and age.[14] As previously demonstrated through epidemiologic research, partner characteristics are significant risk factors in the transmission of STIs and can be furthered explored through sexual NA.

The presence of bridges between components in a sexual network is a key determinant in the spread and maintenance of infection.[32] A bridge is defined as an individual or a group of individuals who serve to connect various components within a sexual network.[32] The amount of disassortative mixing between high and low risk components of a sexual network determines whether infections remain in core groups or are disseminated throughout the sexual network.[149] An individual's position as a bridge is determined quantitatively by the individual network measure betweenness centrality.[136]

An individual with a high betweenness centrality score serves as a conduit of transmission between individuals in the same network who otherwise would not be connected.[136,137] Additional measures of individual centrality include degree, eigenvector, two-reach and closeness centrality (see section 3.4.2.2 Individual Network Centrality).

Laumann and colleagues conducted a nationally based sexual NA in the US in order to identify the sexual network characteristics of the defined population.[54] Two noteworthy findings were the significantly greater amount of bacterial infections reported by females and black individuals. Laumann *et al*. proposed that females have higher infection rates than males since the females' male partners generally had higher numbers of sexual encounters than the males' female partners.[54] Therefore, the features of female partners served as a greater risk factor than their individual attributes.[54] Intra- and interracial sexual networks were analyzed to identify the cause of increased risk in black individuals.

Intra-racial sexual networks compared the amount of interaction between individuals who were defined as the periphery (one sexual partner in the last 12 months) and the core (a minimum of four sexual partners in the last 12 months) while adjusting for known risk factors in specific racial/ethnic groups. Results indicated that black individuals on the periphery were five times more likely to have a core sexual partner compared with whites and four times more likely than Hispanics.[54] Therefore, a black individual with limited sexual partners is at greater risk of infection due to their partner characteristics compared with their white and Hispanic counterparts. Lastly, the highly interracial assortative mixing observed amongst black individuals (i.e., more likely to engage in sexual contact with another black individual) explains the maintenance of

higher infection rates within individuals who are black.[54] These findings suggest that the observed increase in infection in black individuals is a result of the highly disassortative intra-racial and assortative interracial partner mixing. Similarly, black adolescents who engage in sexual activity with core network members were found to be at an increased risk of STIs[55] and teens who interact with members of different races/ethnicities (disassortative mixing) were also at an increased risk for an STI.[146] Although partner mixing, observed by Laumann *et al.*, and bridges have been identified as important, limited research has utilized the network approach with the objective of quantifying the extent to which partner characteristics and bridges influence transmission therefore, further research is warranted.

Concurrency in a sexual network occurs when an individual has multiple sexual relationships, which overlap in time.[147] Concurrent sexual relationships are widespread and have led to the investigation of the impact on STI transmission in sexual networks.[22,32] Mathematical models replicating HIV transmission have demonstrated that as the proportion of concurrent relationships increases, uniform increases are observed in incidence rates.[150,151] Empirical evidence has also demonstrated that an individual's risk of gonococcal and chlamydial infections increases in a sexual network with a high proportion of concurrent relationships.[30]

Lastly, varying network positions have also been associated with a greater likelihood of acquiring a STI.[24] By simulating the spread of STIs, a number of studies have identified the association between individual centrality and an increased risk of infection.[140,152] Additionally, risk-potential NA of injection drug users and HIV identified core and inner periphery members as having the highest rates of infection.[134] Most

recently, empirical research has demonstrated an associated between a central network position and gonorrhea.[143,153]

2.15.3 Prevention and Control Strategies

Extensive research has identified the significant influence social networks have on the degree of risk when engaging in injection drug use.[148] Accordingly, network-level approaches have been employed and have successfully led to a reduction in the use of risky injection drug use in these networks.[148] Limited attention however, has been placed on the influence of networks on sexual risk reduction practices despite the recognition of the importance of social/sexual networks in the spread of STIs.[148] Nonetheless, preliminary network approaches developed through NA have provided optimism in improving STI prevention/control strategies by identifying sexual network determinants, vulnerable individuals missed through traditional core group identification and novel network-based interventions.

2.15.3.1 Social Determinants

Approaching the spread of STIs from a network perspective also involves the identification of social determinants of sexual networks in order to reveal the underlying cause of sustained transmission.[22] Residential location and mutual frequenting of specific social establishments have been identified through sexual NA as important determinants in the development of sexual networks.[22] Accordingly, the identification of the aforementioned determinants provides insight into the important sources of spread in an outbreak, epidemic or endemic setting.[22,31,143]

2.15.3.2 Greater Outreach

When developing prevention/control strategies for STIs, it has previously been demonstrated in high-risk HIV populations, that network-based interventions are able to reach a greater number of vulnerable individuals and build on the limitations of current community-based interventions.[154] The success of network-based interventions lies in the ability to effectively reach a significant portion of the infectious and susceptible population. Individuals who are not overtly part of a defined community or involved in a sexual network where an established social aggregation site does not exist, can be targeted through the previously established network structures.[155] The identification of networks improves the probability that individuals, who would otherwise be overlooked, will be reached through non-conventional prevention/control strategies.[154]

2.15.3.3 Network-Based Interventions

The network approach is focused on reaching members through their connections with others and relies on the established social environment created through social networks to influence risk reduction behaviour.[148,154] The environment and behavioural norms of a social network are influenced by the internal attributes of network members since they are commonly comprised of individuals with similar characteristics and behavioural norms.[156] Moreover, social networks provide trust and support to members and thus, further influence shared values and beliefs.[156] Aside from theoretical evidence, empirical data have underscored the importance of a social network in predicting high-risk sexual practices. Previous research has demonstrated that the social network to which an individual belonged was the strongest predictor of risky sexual behaviour compared with

individual-level factors including safe sex knowledge, attitudes and intentions.[148,154-157] Members of a particular social network were found to have similar levels of risky sexual behaviour including unprotected sex, exchanging sex for money and having multiple partners.[155] Therefore, the social environment and shared behavioural norms of a specific social network impact individuals based on their membership. The social relationships, which promote the development of sexual networks, play an integral role in risky sexual behaviour and thus disease transmission. The knowledge of shared behaviour within a social network has influenced the development of several network-based approaches focused on altering the social norms within high-risk sexual networks.

Social network-based interventions have been shown to successfully disseminate safe sex practices throughout a sexual network and influence common behaviour.[154,155,158] Several methods have been employed to obtain these results including identification and counselling of social network leaders,[158,159] providing network wide peer outreach[160] and influencing individuals to withdraw from a sexual network[155]. The counselled leaders were influenced to share information they learned through peer based counselling with other network members whereas peer outreach involved the identification of social network members (irrespective of network position) followed by risk reduction counselling.[160] By targeting existing network leaders and members, the prevention strategies capitalize on a pre-existing social network where risk reduction norms were easily disseminated throughout the network.[154,158,160]

The aforementioned findings were derived through the analysis of HIV related social networks and their impact on sexual networks. The success experienced through social NA and interventions warrants further investigation of sexual-network based

interventions since, they are formed on the basis of an underlying social network and the identification of these sexual networks can be accomplished through the analysis of notifiable disease data. [161]

2.16 Gonococcal-Network Analysis

STI transmission is influenced by the association between evolving pathogens and complex human behaviour and relationships.[142] Pathogens possess unique virulence factors, which determine the ideal host, site of infection, transmission efficiency and duration of infectiousness resulting in unique transmission across various STIs.[129] Accordingly, sexual network characteristics differ between pathogens, which highlights the importance of identifying network structure and network-based risk factors for each STI individually. [14,25]

N. gonorrhoeae is a highly adaptable pathogen transmitted through mucosal contact of the urogenital, anogenital and oral regions of sexual partners. The period of infectiousness is determined by sex specific incubation periods and the onset of symptomatic or asymptomatic infections.[10,47,142] The lack of protective immunity following infection aids in gonococcal survival and greatly inhibits the ability to develop an effective vaccine.[142] Sexual networks specific to gonorrhea rely on the interplay of gonococcal characteristics and diverse human sexual behaviour. Utilizing sexual NA in various populations and from multiple perspectives has enhanced the understanding of gonococcal spread and persistence over the past two decades. Furthering the knowledge of gonococcal transmission will influence the development of effective control/ prevention interventions required to prevent the spread of the recently emerged EDR

gonococcal strains. The network specific risk factors of gonorrhea identified to date will be discussed.

2.16.1 Network Structure and Core Groups

In populations experiencing endemic levels of gonorrhea, network structures primarily observed have been fragmented (a large number of detached components), linear structures with limited interconnectivity between components.[24,25] The abovementioned structures are consistent with slow yet maintained propagation of infectious diseases.[146] Detailed analysis of the 23 largest sexual network components, including 10 or more individuals, in the province of Manitoba, Canada revealed two distinct sexual network structures; linear and radial structures.[25] Case and contact information was gathered through province wide routinely collected contact tracing data during a period with endemic levels of gonorrhea and chlamydia. Radial components in the present study included central actors with a degree (i.e., number of sexual partners) ranging from five to 13 and sexual partners had an average degree of one.[25] Cases of gonorrhea however were only present in linear structures, which included a number of individuals in sequence with fewer sexual contacts, whereas chlamydial infections were found in both component types. Assortative mixing, a number of individuals from multiple geographic locations and a significant proportion of positive cases were observed in linear components.[25] Similarly, Fichtenberg *et al*. revealed small, acyclic, linear branching structures in the components analyzed in a sample of black adolescents in San Francisco, US with endemic rates of chlamydia and gonorrhea.[24]

The network structures observed in the sexual networks of gonorrhea in Sheffield, UK also identified that the majority of components were small (dyads, triads and components with less than five individuals) and lacked interconnectivity.[162] One out of the three large components (>5) observed in Sheffield resembled a radial structure deviating from the linear structures of the other two components. Nonetheless, the data were greatly limited by missing contact information, which may have resulted in inaccurate sexual network structure representation.[26,162] The limited number of larger linear components identifies the importance of these structures in endemic transmission and supports previous research demonstrating the absence of highly interconnected, cyclical networks in endemic settings.[63,146,163] The findings also support the concept of a core group of highly sexual active individuals, represented by the fewer larger components within the entire sexual network responsible for the persistence of endemic transmission.[26]

Contrarily, highly interconnected, cyclical sexual network structures have been identified in populations during epidemic levels and outbreaks of gonorrhea, chlamydia and syphilis.[63,146,163] Through sexual NA a highly interconnected sexual network including 410 individuals with reported local gang affiliation was identified during an outbreak of resistant gonorrhea in Colorado Springs, US.[27] The core group included 0.1% of the population and was responsible for 22% of all gonorrhea cases reported in the 16-month period.[27] The findings support the notion of the core concept and unequal distribution of gonococcal infection.[27] Consistent with previous findings,[63,146,163] the network structure identified during the gonococcal outbreak was highly interconnected with a predominantly cyclical pattern.[27]

Core groups have been identified as key subgroups involved in the transmission of gonorrhea in both endemic and epidemic settings, however, the difference lies in the network structures during various stages of transmission and are an important consideration in STI prevention and control. In addition to the identification of sexual network structure during specific STI stages, analysis of partner mixing patterns provides a superior understanding of the factors contributing to enhanced/reduced transmission.

2.16.2 Partner Mixing and Bridges

Mathematical models are used to explore sexual networks and individual network-member characteristics in order to better understand STI transmission dynamics. Mathematical simulation models of gonococcal spread in a closed population suggest the most important aspects of partner mixing involve mutual non-monogamous pairs and partnerships with highly sexually active members.[28]

Empirical research supports the importance of identifying partner mixing characteristics in order to further understand gonococcal transmission. Aral *et al.* determined the patterns of sexual partner mixing in a heterosexual population in Seattle, Washington.[32] Although assortative mixing was primarily observed, disassortative mixing patterns were significantly associated with both an increased and decreased risk of gonococcal infection dependent on both individual and partner characteristics.[32] Interracial partnerships were associated with an increased risk of infection with the greatest increase observed in partnerships with black individuals.[32] The following sexual relationships were also associated with an increased risk: sexual partnerships with individuals with a lower educational status, individuals who were 30 years or older who

reported sexual contact with individuals 19 years of age or younger and individuals who reported having one to two sexual partners who engaged in sexual contact with individuals with a greater number of partners. Individuals with three or more partners who reported sex with fewer partners were at a decreased risk.[32]

The predictors of risk in the empirical study were primarily societal features (race/ethnicity, age and educational status) contrary to the findings of the aforementioned mathematical model, which concluded risk-taking behaviour characteristics (non-monogamous pairs and high number of sexual partners) as the most important mixing-features in the risk of infection.[28] The observed difference in mixing patterns is a result of the methodologies used and the variation in the sample characteristics. Nonetheless, both studies reflect the importance of partner identification as an important determinant of transmission.

In addition to partner mixing, Aral *et al.* also observed the importance of individuals serving as bridges of transmission between high and low prevalence subpopulations.[32] The rates of gonorrhea were lower in low-prevalence subpopulations lacking sexual partnerships with high prevalence subpopulations compared with low-prevalence subpopulations with identified bridges.[32] The study findings revealed that the most significant burden in low-prevalence populations was the presence of direct links to individuals in high-prevalence subpopulations.[32] Mixing patterns and bridging within sexual networks is an important consideration when developing prevention/control strategies.[32]

2.16.3 Concurrency

As previously stated, concurrent sexual partnerships have been identified as a predictive factor in STI transmission. Mathematical models have previously found an association between an increased proportion of concurrent partnerships within a population and an increase in the spread of gonorrhea and individual risk, while holding the number of sexual partners constant.[28] Sexual NA of adolescents in San Francisco, US revealed similar findings where a significant association between the proportion of concurrent sexual relationships and gonorrhea diagnosis was observed while controlling for the number of sexual partners and race/ethnicity.[30] Additionally, the high rates of concurrency in adolescent populations are hypothesized to be the cause of the maintained prevalence of gonorrhea in this age category.[30]

2.16.4 Network Position

In addition to network bridges, a number of approaches have been developed to classify various network positions within a sexual network and the associated risk of gonorrhea. Following network position classification, traditional epidemiological risk factors have been compared between individuals in various network positions aimed at determining risk factors associated with high-risk positions.[24,143,146,153,164] Network position classified by component size was initially used as a method of determining the association between network position and gonorrhea. Potterat *et al.* for example, compared individuals in the largest components with individuals in medium and small sized components.[146] This analysis involves a network structure-level method where all individuals are considered to share similar attributes within components stratified by size. Although significant

differences between components of varying size have been identified, variation in network position within components is not incorporated in the analysis.[146]

More recently, network position analysis has involved individual network measures of centrality used to distinguish central and non-central positions within components.[153] Measures of centrality (degree, betweenness and closeness centrality) were used in a sexual NA of a gonorrhea outbreak in Alberta, Canada.[143] Participants with significantly higher closeness centrality were found to have frequented a common motel bar. Follow-up NA of the individuals who patronized the bar demonstrated that the larger components initially identified were all connected by individuals who attended the bar.[143] Additionally, the aforementioned individuals were more likely to have gonorrhea.[143] Variation in network centrality has also been used to explain gender differences in the risk of gonorrhea.[24,54] A sexual NA of black adolescents in San Francisco, US identified females as being less likely to be defined as central using local measures of centrality (i.e., degree and betweenness centrality) however, similarity in centrality was observed while taking the entire network structure (i.e., eigenvector, reach and closeness centrality) into consideration.[24] The variation in centrality explains the increased risk observed in females despite a limited number of sexual partners when compared with males. Specifically, females appear to be at a decreased risk as a result of fewer sexual partners however, analysis of centrality while incorporating the entire sexual network accurately identifies the risky position of females due to their male partners' connections.[24]

Most recently, Fichtenberg and colleagues developed a novel composite variable, incorporating degree and two-reach centrality, used to classify network position.[153]

Network positions included members of dyads, the periphery of components with greater than two individuals, the centre of components with complete centralization (radial components) and the interior of non-radial components.[153] Membership in the interior of components was significantly associated with an increased risk of gonorrhea.[153]

2.16.5 Spatial Relationships

The importance of spatial relationships was first realized following the application of social NA in Colorado Springs, US; an area burdened with a high prevalence of gonorrhea.[31] Through sexual NA, Potterat *et al.* identified four core geographic locations of residency, representing 5.9% of the defined geographic districts, which included all infected cases over a six-month period.[31] Distinct patterns of social aggregation at specific public venues were also identified between heterosexual and homosexual cases and their sexual partners.[31] These findings support the notion that stable social groups (i.e., core groups), established through shared characteristics and geographic location, maintain infection in a population through intragroup sexual encounters.[31]

Similarly, NA examining the spread of gonorrhea during outbreaks in neighbouring reserves in Alberta, Canada revealed the importance of social venues as a channel of disease exchange.[143] As previously mentioned, attendance at a single motel bar was identified as the primary risk factor for infection during the outbreak in all of the neighbouring communities.[143] Additionally, outbreaks perceived to be isolated were linked through individuals in separate communities attending the single motel bar. The underlying source of connection between communities through the motel bar would have been overlooked if the outbreak was analyzed using a traditional epidemiological

approach.[143] The ability to identify the determinants of sexual networks provides the information needed to target specific high-risk areas.[22] Contrary to what was observed in Colorado Springs and Alberta, the widespread distribution of cases and contacts observed within gonococcal-sexual networks in Manitoba, Canada suggests a lack of a defined social aggregation venue and geographic clustering.[25] The variation in results identifies differences in the determinants of sexual networks between various populations.

2.16.6 Prevention

Mathematical modeling of a number of prevention strategies for gonorrhea was able to achieve an effective reduction in the prevalence of gonorrhea.[47] Successful prevention simulations included contact tracing, screening and improved condom use. Contact tracing and screening were designed to treat asymptomatic sexual partners while condom use was intended to reduce the transmission of gonorrhea. In the simulated gonococcal network, gonorrhea was removed from the population by contact tracing when 25% of the identified sexual partners were treated. Screening of high-risk individuals was the most effective following the identification of core groups.[47] Additionally, improved condom use significantly reduced the prevalence of gonorrhea.[47]

The success of previously used social network-based interventions combined with the abovementioned simulated findings, highlight the possibility of effectively utilizing sexual NA to identify and target core groups with the objective of improving prevention/ control strategies. Identification of core members in a sexual network could potentially be used to provide safe sex counselling to these individuals which would likely result in the dissemination of information throughout the sexual network as was previously seen in

social network-based interventions.

2.17 Rationale

The importance of enhanced gonorrhea surveillance is highlighted by the extraordinary capacity of *N. gonorrhoeae* to repeatedly develop resistance against newly introduced first-line treatment options. The delay in collation, analysis and reporting of national and provincial surveillance data in the face of EDR strains, emphasizes the need to promote detailed analysis of local surveillance data.[6,165] Analysis of local surveillance data has the potential to provide a more in depth, representative and timely understanding of gonococcal transmission, which greatly contributes to the decisions of first-line treatment recommendations enabling rapid and effective treatment of infected individuals.[6] The observed variation in sexual behaviour and demographic characteristics between localized populations further highlights the importance of conducting detailed analysis of local surveillance in order to develop the most effective prevention/control strategies.[14] Identifying differences in population composition and the epidemiology of gonorrhea is the most feasible and useful across local populations.[32]

Sexual NA provides a novel, localized method of analyzing surveillance data, which can be used to determine the incidence of gonorrhea and individual risk factors while providing an understanding of the complex sexual relationship structures in a given population. Sexual NA builds on the core group notion by identifying the underlying sexual networks responsible for the maintenance of the high-risk subpopulations. Further research is required to build on the previous success of gonococcal-NA, which has successfully identified the phase of infection, high-risk network characteristics and core

groups in various populations burdened with gonorrhea.

The region under investigation is currently facing a surge in gonococcal infections and necessitates increased analysis of surveillance data and effective prevention/control strategies in order to mitigate the current gonorrhea burden. In attempts to overcome the limitations currently faced by surveillance systems in Canada, novel, localized strategies are essential in prolonging the effectiveness of ESCs. The persistence of gonorrhea and recent spike in incidence in the region of focus provides a fruitful research environment where NA can be implemented and assessed as a local strategy of analyzing gonococcal surveillance data.

2.17.1 Study Aim

This project aimed to identify both network structure characteristics and network positions associated with gonorrhea together with traditional epidemiological risk factor analysis of a population represented by a PHU in Ontario, Canada. The study aimed to investigate the following research question: Are network-based risk factors associated with gonococcal transmission?

CHAPTER III – METHODS

3.1 Data Source

In Ontario under the HPPA, confirmed (detected in clinical specimen) and probable (signs/symptoms in a person with an epidemiological link to a laboratory-confirmed case) cases of gonorrhea are reported to the PHUs in Ontario.[95] PHUs manage the cases and named contacts of individuals with an address within the allotted region. Both case and contact information is input into the iPHIS, which can be accessed by both PHO and the MOHLTC. PHO and the MOHLTC have developed and routinely update a list of disease specific risk factors, which are mandatory for confirmed cases of reportable diseases in Ontario.[166]

Local PHUs are required to report risk factors for identified cases in the iPHIS and are instructed to consult the iPHIS Risk Factor Guide during case investigation and data entry to support the collection of complete and consistent risk factor data.[94] All mandatory risk factors in the iPHIS are associated with a checkbox selected to indicate the individual has a specific risk factor. Additional mandatory fields of reporting in the iPHIS include patient demographics (age and gender) and specific characteristics of the STI encounter. A list of reported sexual partners within 60 days of gonorrhea confirmation is also obtained from each case.[94] The contact database includes the information of index cases who identified the contact, demographic variables (age and gender) and the dates during which exposure took place.[94] The previously mentioned risk factors are included if the named sexual partner was successfully contacted despite the outcome of diagnosis.

3.2 Study Population

The study sample was extracted from the iPHIS surveillance database of a PHU in Ontario, including individuals reported as having gonorrhea along with their named sexual partners between January 1st, 2013 and December 31st, 2014. The PHU in which the data were gathered is defined as an urban/rural mix with an average percentage of Aboriginal people, low male population and slow population growth between 1996 and 2001.[167]

A positive gonorrhea status defined by the PHU in the current study included individuals with either a laboratory confirmed diagnosis or those with signs/symptoms and an epidemiological link to an infected individual. The data included routine gonorrhea-specific information collected from both patients diagnosed with gonorrhea and their reported sexual partners. The data, which were analyzed in the study, are the most accurate and representative information available for gonorrhea cases and sexual partners. Research Ethics Board approval was obtained from both Brock University and the PHU. A data sharing agreement was created and agreed upon by both Brock University and the PHU. Removing participant identifiers from the data prior to analysis ensured anonymity.

3.3 Statistical Analysis

Bivariate and multivariate analysis of demographic variables and gonorrhea-specific risk factors was completed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). As a result of a lack of independence between participants found in common components, logistic and linear regression with generalized estimating equations (GEE) were used to control for

correlated data.[168] Sexual networks were constructed and network measures calculated using UCINET VI (UCINET for Windows: Software for Social Network Analysis. Harvard, MA: Analytic Technologies). Statistical analysis was modeled after a number of studies, which had a similar focus.[22,24,29,143,148,153,164]

3.3.1 Study Variables

The following case/contact information, demographic variables and risk factors were gathered from the iPHIS surveillance database and included in the statistical analysis. *Case/Contact:* consistent with sexual NA classification, cases were defined as individuals with gonorrhea who were followed up by a public health nurse due to the development of symptoms specific to gonorrhea. Contacts were defined as individuals who were contacted by a public health nurse after being named as a sexual contact of a case. A case that was subsequently named a contact included individuals who were initially defined as a case and reappeared in the dataset as a contact. Lastly, a contact subsequently named a case was a named contact that tested positive for gonorrhea and was then defined as a case according to the public health definition.

Demographic Variables: age and gender. *Behavioural/Social Risk Factors*: anonymous sex, condom breakage, judgment impaired by alcohol/drugs, number of sexual contacts in the last six months, new contact in past two months, no condom use, sex trade worker, sex with sex trade worker, sex with the opposite sex, sex with the same sex, contact is HIV positive, use of sex toys, contact is visiting outside of province and met contact over the internet. *Medical Risk Factors*: HIV status, repeat STI, co-diagnosis/co-infection with existing STI and whether a female was pregnant. *Exposure*

Setting Risk Factors: attending a bathhouse, correctional facility (incarceration), other social venue, travel outside of province and being homeless. The risk factors were selected as a result of relevancy with the current study population and are consistent with the literature. For a complete list of the gonorrhea-specific risk factors gathered through the iPHIS database see Appendix B.

3.3.2 Descriptive Statistics of Study Participants

Detailed analysis of the gonorrhea encounter, demographic and risk factor characteristics for the entire population was summarized (Appendix C Table C.1.1 and Table C.1.2). Study variables representing the confirmation of gonorrhea status and availability of risk factor data for the entire sample were required to determine participant inclusion in follow-up analysis.

3.4 Sexual Network Analysis Protocol

This section provides a summary of the sexual NA methodology employed in the current study. A detailed description will be provided in the subsequent sections.

Stage 1 Network components within the sample were identified.

Stage 2 Network Measure Analysis

2.1 NETWORK STRUCTURE: Network components were characterized based on size, topology, interconnectivity (density, diameter, *k*-cores and cliques) and centralization (degree, closeness, betweenness and eigenvector centralization).

2.2 INDIVIDUAL NETWORK CENTRALITY: Individual measures of centrality (degree, eigenvector, two-reach, closeness and betweenness centrality) were computed and stratified by component size.

Stage 3 Exploratory analysis was used to analyze the association between network structure/individual measures of centrality and gonorrhea status. The significant association between individual measures of centrality and gonorrhea status in addition to, the observation of a positive gonorrhea status in central members of radial structures influenced further investigation of network position and associated risk factors.

Stage 4 Network position (central and non-central) within components was determined through a composite variable including degree and two-reach centrality. Following the identification of network position, the measures of centrality were compared between central and non-central positions.

Stage 5 Epidemiological risk factors were compared between individuals classified by network position. Significant differences between demographic variables and risk factors were determined using simple linear regression with GEE for continuous data and logistic regression with GEE for categorical variables.

Stage 6 Bivariate and multivariate logistic regression with GEE was performed to determine the demographic variables and risk factors significantly associated with network position.

Stage 7 Partner mixing with respect to age and number of risk factors reported was analyzed in order to determine the importance in the transmission of gonorrhea.

Stage 8 The means of both the network structure/individual measures of centrality for the entire sample were reported to represent the entire sexual network structure of gonorrhea cases and named sexual contacts in the sample.

3.4.1 Stage 1 – Component Identification

The initial stage of the NA involved the identification and graphing of network components within the defined sample. A component in a sexual network consists of a group of individuals who are connected directly or indirectly with one another.[147] Similar to previous research, a sexual partnership was considered to exist if mentioned by at least one of the sexual partners.[24,153] Therefore, network components were analyzed as undirected (symmetric) graphs.[136] Records of sexual contacts were obtained from the iPHIS database and a spreadsheet was created containing line-listed records of sexual relationships.[25] The newly created spreadsheet was imported into UCINET, which was then reformatted into an adjacency matrix.[136] An adjacency matrix of an undirected graph includes an identical list of nodes in both the rows (i) and columns (j). The bottom left and top right of the adjacency matrix, divided by the main diagonal, include matching data therefore, $x_{ij} = x_{ji}$ where x represents the matrix.[136] Each entry in the adjacency matrix (i, j) represents either a sexual relationship denoted by $x_{ij} = 1$ or a lack of relationship $x_{ij} = 0$. The adjacency matrix was used to graph and analyze the network components.[136]

3.4.2 Stage 2 – Network Measure Analysis

Sexual NA utilizes network theory methodology in order to investigate the role network components of various structures and individuals with various network positions have in the transmission of STIs in a defined population.[134] The distinct levels of analysis have corresponding network measures, which provide a quantifiable understanding of networks and are used for objective comparisons. Network component measures, referred

to as network structure measures, further the understanding of STI transmission by providing information regarding the properties of the structure of a cluster of sexually connected individuals.[146] Whereas, individual level measures, referred to as measures of centrality, determine an individual's position within a larger sexual network.[147]

3.4.2.1 Stage 2.1 – Network Structure

The components identified in *Stage 1* were characterized based on size, topology, interconnectivity (density, diameter, *k*-cores and cliques) and centralization (degree, closeness, betweenness and eigenvector centralization) using network metrics previously found to be relevant to STI transmission.[22,24,25,29,143,148]

3.4.2.1.1 Size

Partitioning of the dataset in UCINET IV enabled analysis of distinct components. The size of the network components were determined and accompanied by the frequency of each component of size *n* and the proportion of network members in each component of size *n*.

3.4.2.1.2 Topology

The network topology of components with three or more members was determined visually to be linear, radial or cyclical structures. Component structure was analyzed in order to predict the stage of gonococcal infection (endemic, epidemic or outbreak) in the defined region.[22]

3.4.2.1.3 Interconnectivity

Component interconnectivity was analyzed by computing density and diameter and through the identification of specific network structures including *k*-cores and cliques. Density describes the total number of observed edges in a network relative to the total number of possible edges and is expressed as follows:

$$Density = \frac{Observed\ number\ of\ edges}{[n(n-1)]/2},$$

where *n* is the number of nodes included in the component.[136] The diameter of a network is defined as the length of the longest shortest path in a network.[24] This describes direct and indirect pathways between network-members and does not focus on the measurable distance between nodes.[147] The diameter of a component provides a description of the overall structure of the network; low scores represent a cohesive network since the length between network members is short while high scores represent a less cohesive network.[147]

A *k*-core defines a specific type of component where each node has a minimum degree (i.e., the number of connections) of *k* with a minimum degree of 2.[136] Within a *k*-core each individual in the component is connected to at least *k* other people. *K*-core analysis is helpful in determining whether the network component reflects an interconnected structure.[147] A clique defines a highly interconnected component of three or more individuals who are directly connected to one another.[134,147] The interconnectivity of a component was determined through a combined analysis of density, diameter, *k*-cores and cliques.

3.4.2.1.4 Centralization

Centralization measures the extent to which a component represents a centralized structure; whether the network is focused around a single node with the highest individual centrality.[134,147] The term centralization is restricted to component level analysis whereas centrality describes the position of a node within a larger network.

Component centralization was calculated with respect to degree, eigenvector, closeness and betweenness centrality (i.e., how centralized the component was around the node with the highest measure of centrality). Measures of centralization were then stratified by shape in instances where components of size *n* had differing network topology. Various measures of network centralization were conducted to enhance the understanding of component centralization and accurately identify the association with gonorrhea status. Centralization according to each measure of centrality mentioned above was calculated using Freeman's general formula for centralization:

$$C_x = \frac{\sum_{i=1}^{n}[C_x(p^*) - C_x(p_i)]}{max\sum_{i=1}^{n}[C_x(p^*) - C_x(p_i)]} \ ,$$

where $C_x(p_i)$ is a measure of centrality for a given node, $C_x(p^*)$ is the highest measure of centrality in the component under analysis and $max\sum_{i=1}^{n}[C_x(p^*) - C_x(p_i)]$ is the maximum sum of differences of centrality for a graph of *n* nodes.[169] The denominator provides the value which would be achieved if a component had complete centralization around a single node.[169] Freeman's measure of centralization ranges from zero to one where higher values indicate a greater amount of centralization.[169]

3.4.2.2 Stage 2.2 – Individual Network Centrality

The relative importance of each individual in the components was evaluated using the following network measures of centrality: degree, eigenvector, two-reach, closeness and betweenness centrality. The aforementioned measures of centrality have been associated with STI risk in previous research.[24,25,143,153] A number of centrality measures were analyzed in order to accurately categorize network position and determine the association between network position and gonorrhea status.[136] Individual centrality analysis in dyads however, was limited to degree and two-reach centrality since the remaining measures do not provide meaningful results for components of size two.[24]

Degree centrality is the simplest of the centrality measures and defines the number of sexual partners surrounding a node (i.e., number of sexual partners).[143] Degree centrality of node *i* is defined as:

$$d_i = \sum_j x_{ij} \ ,$$

where x_{ij} identifies the presence or absence of sexual relationships in the adjacency matrix.[137,169] Normalized degree centrality is calculated by dividing the observed degree by the maximum degree possible $(n - 1)$ for a component of size *n*. Normalized degree centrality, ranging from zero to one, allows for comparison between components of differing sizes. Caution was taken when determining the mean normalized degree centrality for the sexual network since the results are skewed towards a more central outcome when dyads (with a normalized degree of one) are included in the analysis. Mean degree centrality was computed including and excluding dyads to the account for the skewed results. Degree centrality is beneficial in identifying the number of sexual

partners each participant has, however is restricted to the immediate connections of a node.[170]

Eigenvector centrality was included in the analysis to build on the limitations inherent to degree centrality.[137] Unlike degree, eigenvector centrality weights the connection of a focal node with adjacent nodes based on the centrality of the adjacent nodes.[170] Therefore, the entire network is considered when computing eigenvector centrality and reflects the degree to which a node is connected to other parts of the network with high connectivity. Eigenvector centrality of node *i* is defined as:

$$e_i = \frac{1}{\lambda} \sum_j x_{ij} e_j \ .$$

The computation of eigenvector centrality is an iterative process where e is the eigenvector centrality score (of the focal (i) and adjacent (j) nodes) and λ is a proportionality parameter known as an eigenvalue.[170]

The first step in the calculation of eigenvector centrality involves the assignment of an eigenvector score to each of the neighbours of a focal node. The initial eigenvector centrality of the focal node is subsequently calculated by multiplying one by the assigned centrality score of the focal node's neighbours where one represents a sexual relationship. As a result of a change to the focal node's eigenvector centrality score, the scores of the neighbouring nodes will also change. Consequently, the eigenvector centrality of the focal node must undergo additional computations until convergence is reached.

Convergence (where the values of eigenvector centrality stop changing) is achieved by multiplying $x_{ij}e_j$ by a proportionality parameter defined by the reciprocal of λ. The eigenvalue (λ) is calculated for the adjacency matrix created by $x_{ij}e_j$ for the initial iteration and at each recurrence of the eigenvector centrality computation. The

reciprocal of λ is required to scale the sum during each cycle of eigenvector computation in order to reach convergence during the recursive process of eigenvector centrality computation.[170] The eigenvector centrality assigned to a node is the outcome associated with the largest eigenvalue.[170] Following the computation of the eigenvector centralities in the current study, the scores for each node were normalized to the specific component in which the node was a member, which allowed for comparison across components of various sizes.

Despite the improvements, eigenvector centrality has the potential to overestimate centrality since it does not account for shared relationships between the focal node and adjacent nodes.[136] Two-reach centrality, although a more simplistic measure, was included in the analysis since it accounts for shared relationships between focal and adjacent nodes. Two-reach centrality defines the number of nodes two steps away from the focal node.[136] In sexual network terms, the number of partners' partners each individual has.[24] The simplistic nature of two-reach centrality warrants combined analysis with additional measures of centrality such as degree or closeness centrality in order to accurately interpret two-reach centrality.[136]

Closeness centrality determines the mean distance a node is from every other node included in the component.[147] This measure considers the importance of indirect disease transmission in sexual networks.[143] Closeness centrality of node *i* is defined as:

$$c_i = \frac{1}{\sum_j d(i,j)},$$

where $\sum_j d(i,j)$ represents the farness of a node. Farness is the sum of the lengths of the geodesics (shortest paths) to all other nodes in the component. Multiplying by the

maximum possible closeness ($n-1$) of a given component normalizes the closeness centrality of a node. Values closer to one represent highly central nodes.

Lastly, betweenness centrality is defined as the extent to which a node connects two nodes which otherwise would not be linked in a component.[134] Betweenness centrality is viewed as the extent to which an individual serves as a channel of STI transmission between two otherwise unconnected individuals.[143] Betweenness centrality of node *i* is defined as:

$$b_i = \sum \frac{g_{jik}}{g_{jk}},$$

where g_{jik} is the number of geodesic paths between two nodes (j and k) through the focal node (i), and g_{jk} is the total number of geodesic paths connecting nodes j and k.[136] Betweenness centrality describes the total number of times the focal node falls on the shortest path between each pair of nodes in the component. Normalized betweenness centrality is computed by dividing the betweenness centrality by the maximum possible betweenness [(*n*-1)(*n*-2)/2]. Similar to normalized degree, eigenvector and closeness centrality, values closer to one represent highly central nodes.

The individual measures of centrality were computed to determine network position in the identified components. A combined analysis of the abovementioned centrality measures was required to ensure accurate identification of network position and association with gonorrhea status.

3.4.3 Stage 3 – Association between Network Measures and Gonorrhea

Exploratory analysis through bivariate logistic regression with GEE was conducted to analyze the association between network structure/individual measures of centrality and

gonorrhea status. The association between measures of network structure and gonorrhea status was determined through logistic regression with GEE with gonorrhea status (positive and negative cases) as the dependent variable and measures of network structure as the predictor variables. Component size, density and diameter are the only network structure measures meaningful in components of size two,[24] therefore dyads were not included in the analysis of the remaining measures of centralization including degree, eigenvector, closeness and betweenness centralization.

Similarly, individual measures of centrality were analyzed through bivariate logistic regression with GEE with gonorrhea (positive and negative cases) as the dependent variable and individual centrality measures as the predictor variables. Normalized centrality measures, with the exception of two-reach centrality, were included in the analysis to allow for accurate comparison between components of various sizes.[136]

3.4.4 Stage 4 – Network Position

Network position is determined by a number of centrality measures including degree, eigenvector, two-reach, closeness and betweenness centrality. Recently, Fichtenberg and colleagues determined network position based on a composite network variable including degree and two-reach centrality.[153] After dichotomizing degree (1 vs. ≥ 2) and two-reach centrality (0 vs. ≥ 1), the composite variable was used to classify network position of varying centrality including: (1) dyads (degree = 1 and two-reach-centrality = 0), (2) periphery of non-dyadic components (degree = 1 and two-reach centrality ≥ 1), (3) center

of radial components (degree ≥ 2 and two-reach centrality = 0) and (4) interior of non-radial components (degree ≥ 2 and two-reach centrality ≥ 1).[153]

A similar approach was applied in the current study. After creating the composite variable, network position was classified as central (positions 4 and 5) and non-central (positions 1 and 2). The classification method explained above was used in the current study due to the ability to combine and dichotomize degree and two-reach centrality. Utilization of the remaining centrality measures would require the identification of a study specific cut-point and would prevent generalizability of the classification method. Additionally, normalized degree, eigenvector, closeness and betweenness centrality are not meaningful in dyads.[24] The method of classification was validated across all measures of centrality included in the study. Irrespective of the measure of centrality used in the validation process, the same individuals were consistently classified as central versus non-central when compared with the classification method explained above. Following the identification of network position, differences in measures of centrality (for individuals with a determined gonorrhea status) were compared through linear regression with GEE between central and non-central positions.

The proportion of individuals who would not have been identified as central in the absence of NA was determined by identifying the number of sexual contacts named by individuals in the central network position group. Individuals who reported one or fewer sexual contacts were considered non-central in the absence of sexual NA and were compared to the number of individuals identified as central through NA.

3.4.5 Stage 5 – Risk Factor Analysis

Epidemiological risk factors and demographic variables (see section 3.3.1 Study Variables) were compared between individuals classified by network position (central vs. non-central). Significant differences between demographic variables and risk factors were determined using simple linear regression with GEE for continuous data and logistic regression with GEE for categorical variables. Individuals without risk factor data and/or confirmed gonorrhea status were excluded from the analysis.

3.4.6 Stage 6 – Bivariate and Multivariate Risk Factor Analysis

The association of risk factors between central and non-central network positions was determined through bivariate and multivariate logistic regression. Firstly, variables significant at $p < .10$ in *Stage 5* were further examined through bivariate logistic regression with GEE with network position (central vs. non-central) as the dependent variable and individual risk factors as the predictor variables. Variables significant at $p < .10$ in the bivariate analysis were included in a multivariate logistic regression with GEE while controlling for the potential interaction with other risk factors. A manual stepwise elimination of variables was used to identify risk factors related to network position at $p < .05$ using the quasi-likelihood under the independence model criterion (QIC) analogous to AIC in logistic regression without GEE.[4,168] The reported Odds Ratio (OR) and 95% Confidence Intervals (CI) were used to identify the risk factors, which were significantly associated with membership in central positions.

3.4.7 Stage 7 – Partner Mixing

Partner mixing patterns within the sexual network was determined with respect to the variables age and total number of risk factors. The amount of assortative and disassortative mixing within the network was determined using Moran's *I* statistic for autocorrelation.[171,172] Moran's *I* statistic was computed to determine the amount and direction of correlation between the attributes of individuals who were identified as being in a sexual relationship (x_{ij} = 1) based on the original adjacency matrix.[172] The statistic is computed similarly to the Pearson correlation coefficient with outcomes ranging from -1.0 (perfect negative correlation) to +1.0 (perfect positive correlation) with 0 identifying no correlation.[171]

The statistical significance of the statistic was determined using the permutation method.[172] Each permutation randomly assigns the scores of observed attributes to individuals in the network and recalculates the statistic. The average statistic from all permutations is then compared with the observed statistic and the probability of obtaining a correlation as big or small as the observed statistic is determined.[171,172]

3.4.8 Stage 8 – Summary

The means of both the network component and individual measures of centrality for the entire population were determined in order to provide an analysis of the entire sexual network. The network summary measures of size, diameter, density and degree included dyads in the analysis. Since density is one for components of size two, the mean density for the entire population was calculated with and without dyads.[24] Reporting of summary

findings of network structure and individual measures of centrality will be integrated into Stages 2.1 and 2.2, respectively.

3.5 Additional Analysis

The density for undirected and directed network components were compared with the objective of identifying whether there was a lack of reporting of sexual relationships in the sample. As explained above, undirected graphs were examined throughout the study, which considered a sexual relationship to exist if named by at least one individual. Directed graphs however, indicate who named who in the network and whether the relationship was reciprocal. The density was compared between the directed and undirected networks using a paired *t*-test.

CHAPTER IV – RESULTS

4.1 Participant Description

The complete study sample included 356 participants identified through the iPHIS gonorrhea-specific database. All participants were included in the graphing of the sexual network. Table 4.1 depicts the condensed results of the gonorrhea encounter, demographic and risk factor characteristics of the study participants. Participants had a mean age of 27 years (SD = 10.64) and were more likely to be male (60.12%). The study sample was composed of 191 index cases and 164 named sexual contacts. A single participant met the criteria of both a case and a contact at two distinct time periods. More specifically, 38 (19.90%) of the index cases were subsequently named as a contact whereas 40 (24.39%) sexual contacts were subsequently diagnosed with gonorrhea and identified as a case. Of the individuals with a confirmed gonorrhea status (90.17%), 234 (72.90%) individuals had a positive gonorrhea status. Risk factor data was available for 261 (81.31%) participants. A detailed summary of study participant characteristics can be found in Appendix C (Table C.1.1, C.1.2). Figure 4.1 provides an overview of participant exclusion in follow-up analysis, which was dependent on membership in a component with greater than one individual, a determined gonorrhea status and the availability of risk factor data.

Table 4.1 Participant Description

Frequency (%)	Total
	n =356
Gonorrhea Status	
Confirmed Positive	234 (65.73)
Confirmed Negative	87 (24.44)
Lost to follow-up	35 (0.83)
Detailed Encounter Type	
Case	153 (42.98)
Contact	124 (34.83)
Case subsequently named a contact	38 (10.67)
Contact subsequently named a case	40 (11.24)
Case & Contact at two time points	1 (0.28)
Encounter Type	
Case	191 (53.65)
Contact	164 (46.07)
Case & Contact at two unique time points	1 (0.28)
Age (years)(SD)	26.92 (10.64)
Gender	
Male	193 (60.12)
Female	128 (39.88)
Risk Factors	*n=261*
Risk Factor Data	261 (81.31)

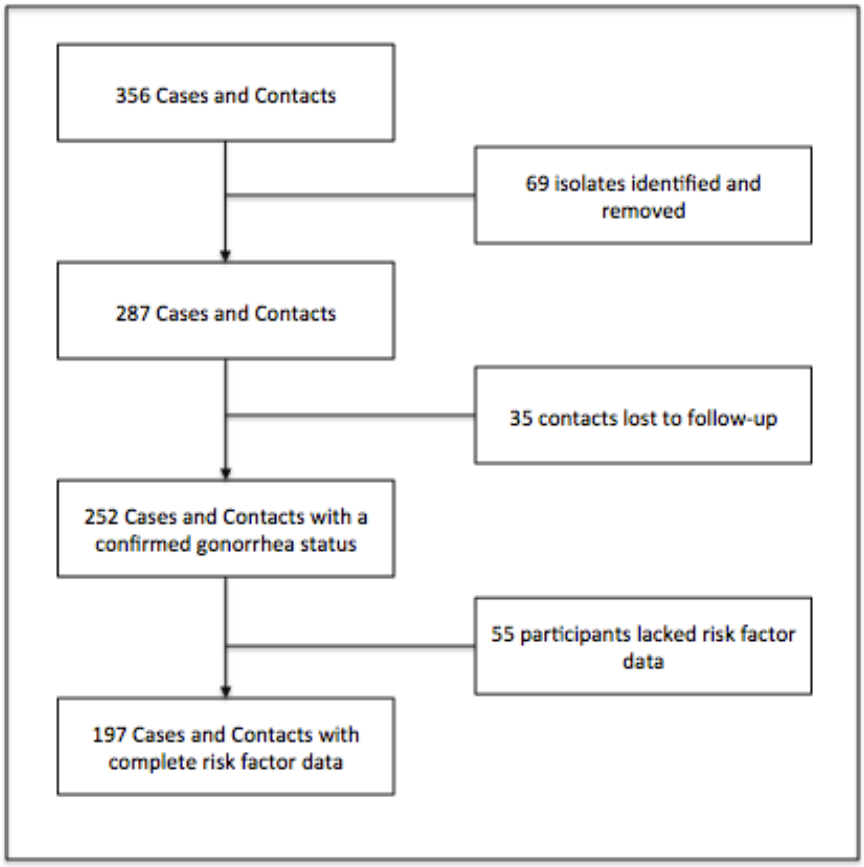

Figure 4.1. Overview of Participant Exclusion Criteria. Participants were excluded from follow-up analysis if identified as an isolate, lost to follow-up resulting in the inability to determine an accurate gonorrhea status and when risk factor information was unavailable.

4.2 Sexual Network Analysis

4.2.1 Stage 1 – Network Components

The sexual network was composed of 175 separate components of which 69 were isolates (component size = 1). The observed isolates were excluded from further analysis since they represent participants with confirmed gonorrhea with incomplete sexual histories who were not named as sexual contacts. Accordingly, 287 participants in a total of 106 components ranging in size from two to 11 underwent further analysis (Table 4.2, Figure 4.1).

Table 4.2 Distribution of Component Sizes

Component Size (*n*)	Frequency of Components (%)	No. of Individuals in Components of Size *n* (%)	Cumulative Frequency (%)
2	74 (69.81)	148 (51.57)	148 (51.57)
3	16 (15.09)	47 (16.72)	196 (68.29)
4	8 (7.55)	32 (11.15)	228 (79.44)
5	3 (2.83)	15 (5.23)	243 (84.67)
6	1 (0.94)	6 (2.09)	249 (86.76)
8	1 (0.94)	8 (2.79)	257 (89.55)
9	1 (0.94)	9 (3.14)	266 (92.68)
10	1 (0.94)	10 (3.48)	275 (96.17)
11	1 (0.94)	11 (3.83)	287 (100.00)
Total	106	287	287

4.2.2 Stage 2 – Network Measures

The following two sections (4.2.2.1 Stage 2.1 – Network Structure and 4.2.2.2 Stage 2.2 – Individual Network Centrality) describe the results of the network measures conducted in the current study. Section 4.2.2.1 provides an overview of the network structure measures including component size, topology, interconnectivity and centralization. Section 4.2.2.2 describes the measures of individual centrality. A summary of the entire network structure (i.e., the means of both the network structure and individual measures of centrality) will also be discussed.

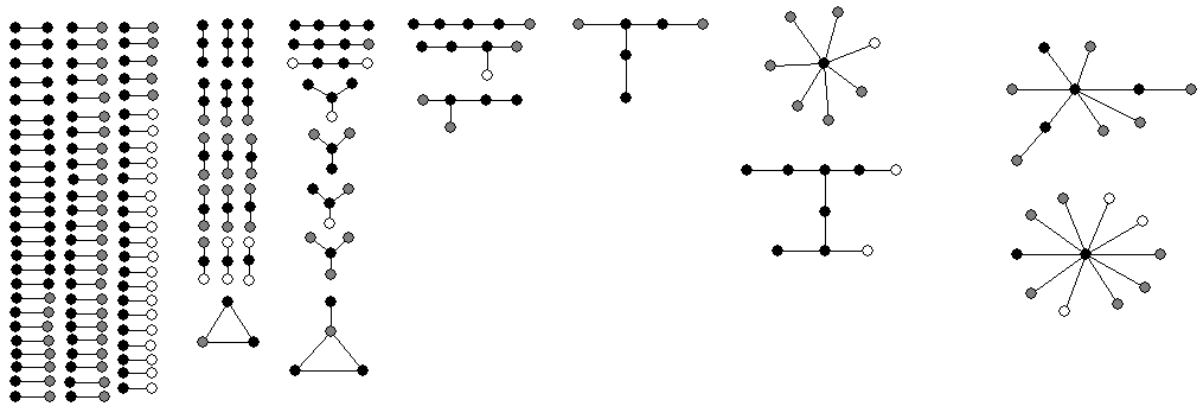

Figure 4.2. Visualization of Sexual Network Components. Nodes represent study participants and the edges between the nodes indicate sexual relationships. The colours identify gonorrhea status: black represents participants with gonorrhea, grey indicates a negative gonorrhea status and white identifies individuals lost to follow-up.

4.2.2.1 Stage 2.1 – Network Structure

The overall sexual network was disconnected with a large number of small components (Figure 4.2). The mean component size was 3.64 (SD = 2.57) however, the majority of the components (84.9%) were dyads and triads (Table 4.2). Despite the large number of smaller components, 16 components with four or more individuals (representing 31.71% of the study sample) were observed. A visual analysis of the topology of components with three or more individuals revealed an assortment of network structures. Triads were primarily linear (15 of the 16 triads) with an exception of one cyclical component. Components composed of four or more individuals were similarly observed to be linear (8 of the 16 components) and radial (7 of the 16 components) structures. Three of the observed linear structures (component sizes = 5 and 6) were branching linear structures and one of the radial structures had two extensions from the central node with greater than one individual (component size = 10). The component with nine individuals included two linear structures with a node serving as a connection between the two main

linear structures. Lastly, a cyclical structure in a component of size four was also observed.

Component measures of interconnectivity and centralization are presented in Table C.2.1 (Appendix C) with measures stratified by component shape in Table C.2.2. Firstly, the density of components decreased as the size increased (r_s = -0.98, p = < .0001), indicating a decrease in the observed number of sexual relationships relative to the total possible number of sexual relationships in larger components. Restricted analysis of larger components (component size six to 11) identified limited variation in density (μ = 0.24, SD = 0.059). Larger, highly dense networks were not identified. The positive correlation observed between component diameter and component size (r_s = 0.97, p = < .0001) represents a similar decrease of interconnectivity in larger components. An increase in diameter reflects an increase in the length of the longest path therefore, a decrease in interconnectivity. Linear and branching linear components had a greater diameter compared with radial structures. Two *2*-cores, which also satisfied the definition of a clique, were identified in components of sizes three and four, reflecting the previously mentioned cyclical structures. The density of the cyclical structures was greater when compared with linear and radial structures of the same component size (Table C.2.2).

As expected, the mean density including isolates (μ = 0.86, SD = 0.23) was greater than analysis excluding components of size two (μ = 0.55, SD = 0.18). The mean diameter was greater (μ = 2.41, SD = 0.84) following the exclusion of dyads (μ = 1.42, SD = 0.79), which reflects a similar overestimation of component interconnectivity when dyads are included in summary analysis.

The correlation between component size and centralization was not as strong when compared with measures of interconnectivity. The mean correlation coefficient between the measures of centralization and component size was -0.51 (SD = 0.013). Despite a moderate negative correlation driven by the large number of triads included in the sample with centralization measures equal to one, a number of larger components had high levels of centralization. Specifically, the components with eight, 10 and 11 individuals had very high centralization around a focal node, which aligns with the topology (radial structure) of the aforementioned components (Table C.2.2). The ranking of components from low to high centralization (0-1) resulted in a very similar order irrespective of the measure of centralization used. This is a result of a lack of larger components in which centralization would differ due to different individuals serving as a focal node within the same component depending on the measure of centrality under investigation. Comparison of the mean component centralization scores revealed a slightly higher degree of centralization around individuals with high eigenvector centrality (μ = 0.86, SD = 0.24) followed by mean betweenness centralization (μ = 0.84, SD = 0.26).

4.2.2.2 Stage 2.2 – Individual Network Centrality

Individual measures of centrality are summarized in Table C.3.1 (Appendix C) and are stratified by component topology in Table C.3.2. Degree centrality increases as component size increases however, the opposite relationship is observed with normalized degree centrality. This explains a mean increase in the number of sexual partners in larger components yet a decrease in the proportion of observed relationships compared with the

maximum number of relationships possible. The moderate positive correlation (r_s = 0.43, p = < .0001) observed between degree centrality and increasing component size reflects variation in the number of sexual partners within larger components. A positive correlation between two-reach centrality and component size (r_s = 0.88, p = < .0001) was also observed. Normalized closeness (r_s = -0.67, p = < .0001) and eigenvector (r_s = -0.68, p = < .0001) centrality had a similar negative moderate correlation with increasing component size. A strong correlation was not identified, which reflects variation in closeness and eigenvector centrality of participants with membership in components of different sizes. Lastly, betweenness centrality was not significantly correlated with component size due to the large number of participants in components of various sizes with a betweenness centrality of zero. Betweenness centrality was greater in linear components whereas, radial components had a greater closeness centrality.

The mean degree centrality for the entire sexual network was 1.31 (SD = 0.91) however, following the exclusion of dyads the degree centrality increased to 1.63 (SD = 1.22). Participants had the highest normalized closeness centrality (μ = 0.67, SD = 0.20) followed by eigenvector centrality (μ = 0.65, SD = 0.24). Participants in the sexual network had the lowest scores for normalized betweenness centrality (μ = 0.27, SD = 0.40) reflecting a limited number of individuals serving as bridges in the network.

4.2.3 Stage 3 – Association between Network Measures and Gonorrhea

Table 4.3 displays the association between network measures and gonorrhea status. A significant association between network centralization and gonorrhea status was observed whereas measures of interconnectivity and component size did not show a significant

relationship. Degree (β = -1.94, CI = -3.18, -0.70), eigenvector (β = -2.77, CI = -5.26, -0.29), closeness (β = -2.25, CI = -3.87, -0.62) and betweenness centralization (β = -2.62, CI = -4.59, -0.66) were significantly associated with gonorrhea status. The association suggests individuals found in radial structures (i.e., network structures with high centralization around the node with the highest degree) are less likely to have a positive gonorrhea status. Nevertheless, the central individuals in all observed radial structures were identified as having a positive gonorrhea status which warrants further investigation with respect to individual centrality and associated risk factors (Figure 4.1).

Table 4.3 Association between Network Structure and Gonorrhea Status

Model	*n*	Parameter Estimate (95% CI)
Degree Centralization	123	-1.94 (-3.18, -0.70)†
Eigenvector Centralization	123	-2.77 (-5.26, -0.29)†
Closeness Centralization	123	-2.25 (-3.87, -0.62)†
Betweenness Centralization	123	-2.62 (-4.59, -0.66)†
Density	252	0.97 (-0.12, 2.07)
Density	123	1.05 (-1.32, 3.41)
Diameter	252	-0.01 (-0.30, 0.28)
Diameter	123	0.41 (-1.10, 0.92)
Component Size	252	-0.20 (-0.46, 0.063)

Note: *n*=123 Each observation represents an individual (dyads were excluded from the analysis)
n=252 Each observation represents an individual (dyads included in the analysis)
^ $p < 0.001$
† $p < 0.05$

Contrarily, the size of the component and interconnectivity (evaluated through density and diameter) was not associated with gonorrhea status. Therefore, in the current

sample there does not appear to be an association between network size/interconnectivity and gonorrhea status.

As previously mentioned (3.4.4 Stage 4 –Network Position), a statistically significant association between gonorrhea status and all measures of individual centrality was observed (Table 4.4). An increase in network centrality was significantly associated with a positive gonorrhea status. As a result, participants were dichotomized into central and non-central positions based on the composite variable encompassing degree and two-reach centrality. Network position was significantly associated (β = 3.31, CI = 1.36, 4.90) with gonorrhea status. Participants in a central position were more likely to have a positive gonorrhea status compared to those in non-central positions. Individuals without a confirmed gonorrhea status were not included in this stage of analysis. Figure 4.3 illustrates network components with network position represented by node shape and gonorrhea status represented by node colour.

Table 4.4 Association between Individual Network Centrality and Gonorrhea Status

Model	*n*	Parameter Estimate (95% CI)
Degree Centrality	252	2.25 (0.70, 3.79)†
Normalized Degree Centrality	252	1.85 (0.84, 2.87)^
Eigenvector Centrality	123	5.35 (3.25, 7.45)^
Two-Reach Centrality	252	-0.31 (-0.46, -0.16)^
Closeness Centrality	123	4.27 (0.95, 7.57)†
Betweenness Centrality	123	7.18 (3.86, 10.50)†
Network Position	252	3.31 (1.36, 4.90)^

Note: *n*=252 Individuals in dyads were included in the analysis.
n=123 Individuals in dyads were excluded from the analysis
^ $p < 0.001$
† $p < 0.05$

In the absence of network analysis, 25.49% of the participants in a central position would not have been identified as central. This was determined by analyzing the number of sexual partners each individual in a central position self-reported. A non-central position according to self-reported sexual partners included individuals who named one or fewer sexual contacts. Thirteen of the central participants, identified through NA, named a single sexual partner or fewer. Furthermore, a paired *t*-test comparing self-reported and network identified number of sexual partners in components of three or greater, resulted in a significant difference (0.93 vs. 1.56, $p < 0.0001$).

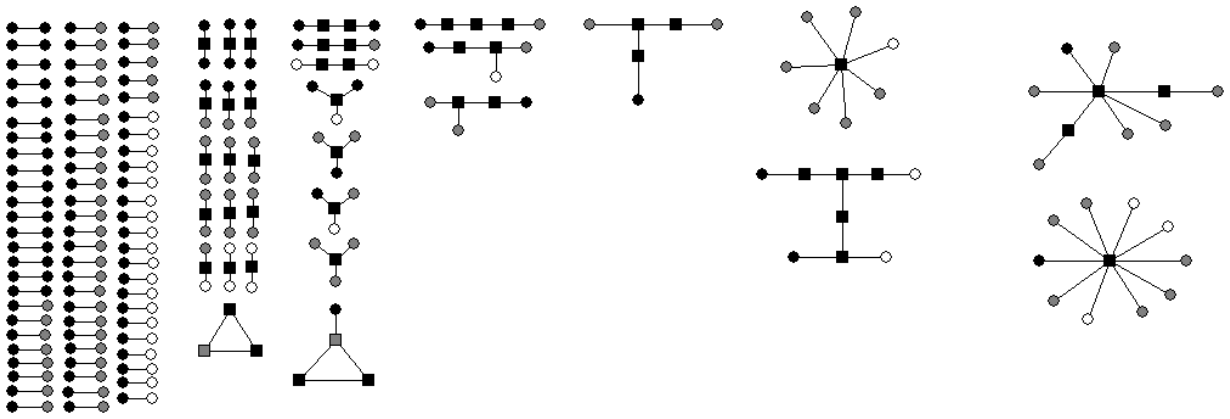

Figure 4.3. Visualization of Network Positions. Nodes represent study participants and the edges between the nodes represent sexual relationships. Colours identify gonorrhea status: black represents participants infected with gonorrhea, grey indicates a negative gonorrhea status and white identifies individuals lost to follow-up. Shape represents network position: squares denote central positions and circles identify non-central positions.

4.2.4 Stage 4 – Network Position

Table 4.5 summarizes the differences in mean centrality measures between central and non-central positions. Significant differences in all centrality measures were found with the exception of two-reach centrality. The non-significant finding is a result of the two-reach centrality score of zero, which is assigned to dyads. An isolated analysis of two-

reach centrality provides an incomplete understanding of the centrality of a node. A two-reach centrality score of zero can be interpreted as a highly central score since the majority of individuals in a larger component are adjacent to the focal node. Contrarily, a low two-reach centrality score can indicate that the focal node does not have a large number of partners' partners because the node is found in a smaller component. Concurrent analysis with another measure of centrality (e.g. degree or component size) is necessary in order to accurately intercept two-reach centrality. The use of a composite method during the classification of network position was further warranted as a result of this finding. The exclusion of dyads when comparing two-reach centrality between network positions resulted in a significant difference.

Table 4.5 Network Centrality Stratified by Network Position

	No. of Individuals			
Mean (SD)	Central	Non-Central	Central	Non-Central
Degree Centrality	51	201	2.53 (1.49)^	1.00 (0)^
Normalized Degree Centrality	51	72	0.75 (0.28)^	0.31 (0.16)^
Two-reach Centrality	51	201	1.02 (1.42)	1.02 (2.22)
Two-reach Centrality	51	72	1.02 (1.42)†	2.86 (2.93)†
Closeness Centrality	51	72	0.82 (0.20)^	0.56 (0.10)^
Betweenness Centrality	51	72	0.69 (0.34)^	0 (0)^
Eigenvector Centrality	51	72	0.85 (0.17)^	0.52 (0.17)^

Note: Individuals without a confirmed gonorrhea status were excluded from the analysis
n=51, *n*=201 Individuals in dyads were included in the analysis
n=51, *n*=72 Individuals in dyads were excluded from the analysis
^ $p < 0.001$
† $p < 0.05$

4.2.5 Stage 5 – Risk Factor Analysis

Table 4.6.1 and 4.6.2 display gonorrhea encounter, demographic and risk factor characteristics of participants stratified by network position. Compared with the non-central individuals, a greater proportion of central individuals had confirmed gonorrhea (96.08 vs. 57.71%, $p < 0.001$) and a smaller proportion were contacts (35.29 vs. 55.22%, $p < 0.05$). Central individuals on average were younger (23.17 vs. 26.98, $p = 0.0729$) and had a greater number of total risk factors (4.00 vs. 2.52, $p < 0.001$). A greater proportion of central individuals had sex with the same sex (23.40 vs. 7.93%, $p < 0.05$), engaged in anonymous sex (19.15 vs. 3.33%, $p < 0.05$), experienced condom breakage (8.51 vs. 2.00%, $p < 0.05$), had greater than one sexual contact in the last six months (70.21 vs. 20.67%, $p < 0.001$) and had a new contact in the past two months (70.21 vs. 35.33%, $p < 0.001$).

Table 4.6.1 Gonorrhea Encounter Characteristics stratified by Network Position

Frequency (%)	Central	Non-Central
	n=51	*n=201*
Gonorrhea Status		
Confirmed Positive	49 (96.08)^	116 (57.71)^
Multiple Gonococcal Infections		
>1 Gonococcal Infection	7 (13.73)	5 (2.49)
Date of Infection/Sexual Relationship		
2013	20 (39.22)	83 (41.29)
2014	27 (52.94)	118 (58.71)
13/14	4 (7.84)	0
Detailed Encounter Type	^	^
Case	18 (35.29)	66 (32.84)
Contact	3 (5.88)	86 (42.79)
Case subsequently named a contact	14 (27.45)	24 (11.94)
Contact subsequently named a case	15 (29.41)	25 (12.44)
Case & Contact at two unique time points	1 (1.96)	0
Encounter Type	†	†
Case	31 (62.75)	90 (44.78)
Contact	18 (35.29)	111 (55.22)
Case & Contact at two unique time points	1 (1.96)	0

Note: Individuals without a confirmed gonorrhea status were excluded

^ $p < 0.001$

† $p < 0.0$

Table 4.6.2 Demographic and Risk Factor Characteristics stratified by Network Position

Frequency (%) (Unless otherwise indicated)	Central	Non-Central
Demographics	*n=51*	*n=201*
Age (SD)	23.17 (7.27) ‡	26.98 (10.85)‡
Gender		
Male	29 (56.86)	115 (45.63)
Female	22 (43.14)	86 (42.79)
Risk Factors	*n*=47	*n*=150
Risk Factor Data		
Available	47 (92.16)†	150 (74.63)†
Risk Factor Group		
Behaviour/Social(BS)	38 (80.85)	125 (83.33)
Medical (M)	0	1 (0.67)
BS & M	9 (19.15)	22 (14.67)
BS & Exposure	0	1 (0.67)
BS, M & Exposure	0	1 (0.67)
Total Risk Factors (SD)	4.00 (1.38)^	2.52 (1.29)^
Reported Risk Factors		
Sex with same sex	11 (23.40) †	13 (7.93)†
Anonymous Sex	9 (19.15) †	5 (3.33)†
Condom breakage	4 (8.51) †	3 (2.00)†
>1 sex contact in the last 6 months	33 (70.21)^	31 (20.67)^
New contact in past two months	33 (70.21)^	53 (35.33)^
Lack of condom use	45 (95.74)	132 (87.33)
Sex with the opposite sex	30 (63.83)	101 (67.33)
Judgment impaired by alcohol/drugs	1 (2.13)	2 (1.33)
Sex trade worker	1 (2.13)	2 (1.33)
Sex with a sex trade worker	1 (2.13)	1 (0.67)
Repeat	10 (21.28)	23 (15.33)
Contact is HIV positive	2 (4.26)	1 (0.67)
Travel outside of province	0	2 (1.33)
Contact visiting outside of province	1 (2.13)	0
Met Contact through the Internet	3 (6.38)	3 (2.00)
Pregnant	0	3 (2.00)
Partner is homosexual	1 (2.13)	0
Strategic positioning	1 (2.13)	0

Note: Individuals without a confirmed gonorrhea status were excluded.

^ $p < 0.001$

† $p < 0.05$

‡ $p < 0.01$

4.2.6 Stage 6 – Bivariate and Multivariate Risk Factor Analysis

Bivariate logistic regression analysis including the aforementioned (*Stage 5*) variables significant at $p < 0.10$ in univariate analysis also resulted in a statistically significant association with network position with the exception of age ($p = 0.0647$) (Table 4.7). Nevertheless, variables significant at $p < .01$ were included in the multivariate analysis.

Table 4.7 Bivariate Logistic Regression Models

Factor *n*=197	Parameter Estimate	OR (95% CI)	*p*-value
Age	-0.055 (-0.11, 0.0033)	0.95 (0.89, 1.00)	0.0647
Total Number of Risk Factors	0.77 (0.46, 1.09)	2.16 (1.56, 2.97)	<.0001
Sex with same sex	1.17 (0.24, 2.10)	3.22 (1.27, 8.18)	0.0139
Anonymous Sex	1.93 (0.86, 2.99)	6.86 (2.37, 19.81)	0.0004
>1 sex contact in the last 6 months	2.37 (1.57, 3.18)	10.78 (4.81, 24.16)	<.0001
New contact is the past 2 months	1.52 (0.75, 2.28)	4.56 (2.12, 9.78)	0.0001
Condom Breakage	1.43 (0.18, 2.68)	4.17 (1.19, 14.59)	0.0252

Note: Individuals without a confirmed gonorrhea status and reported risk factors were excluded from the analysis

Table 4.8 displays the results of the multivariate logistic regression. The variable *Total Number of Risk Factors* was included in a separate multivariate model in order to avoid multicollinearity with additional risk factors included in the model. The first multivariate model indicated that individuals in central positions were more likely to be younger (OR = 0.93, CI = 0.87, 0.10), have anonymous sex (OR = 6.13, CI = 1.33, 28.21), more than one sex contact in the last 6 months (OR = 10.09, CI = 4.45, 22.85) and have sex with the same sex (OR = 4.15, CI = 1.10, 15.67). The second model identified individuals in highly central positions as being more likely to be younger (OR = 0.93, CI = 0.88, 0.99) and have a greater number of risk factors (OR = 2.33, CI = 0.16, 3.30)

compared with non-central individuals. Multicollinearity between covariates was not observed.

Table 4.8 Adjusted Odds Ratios (OR) from Multivariate Logistic Regression Models

Risk Factor *n*=197	Parameter Estimate	Adjusted OR (95% CI)	*p*-value
Model 1			
Anonymous sex	1.81 (0.29, 3.34)	6.13 (1.33, 28.21)	0.0198
>1 sex contact in the last 6 months	2.31 (1.49, 3.13)	10.09 (4.45, 22.85)	<.0001
Sex with Same Sex	1.42 (0.096, 2.75)	4.15 (1.10, 15.67)	0.0356
Age	-0.073 (-0.14, -0.0020)	0.93 (0.87, 0.10)	0.0438
Model 2			
Age	-0.070 (-0.13, -0.0077)	0.93 (0.88, 0.99)	0.0276
Total Risk Factors	0.85 (0.50, 1.19)	2.33 (0.16, 3.30)	<.0001

Note: Individuals without a confirmed gonorrhea status and reported risk factors were excluded from the analysis

4.2.7 Stage 7 – Partner Mixing

A positive autocorrelation between the age ($I = 0.61$, $p < .0001$) of sexual partners was observed. A positive correlation describes assortative mixing with respect to age in adjacent individuals (i.e., individuals similar in age engaged in sexual relationships). Partner mixing with respect to the total number of risk factors did not result in a significant correlation ($I = 0.084$, $p = 0.106$) therefore, the number of risk factors reported by a participant does not influence partner mixing.

4.3 Additional Analysis

The mean density compared between the undirected (symmetric) and directed (asymmetric) network components resulted in a significant difference (dyads included: $\mu = 0.3570$, $p < .0001$) (dyads excluded: $\mu = 0.2137$, $p < .0001$). The significant difference indicates incomplete sexual history reporting within the sample (Table 4.9).

Table 4.9 Mean Density Compared Between Undirected and Directed Networks

Component Size	No. of Individuals (*n*)	Undirected Density (SD)	Directed Density (SD)
2	148	1.00 (0)	0.58 (0.19)
3	48	0. 69 (0.083)	0.47 (0.12)
4	32	0.52 (0.059)	0.32 (0.053)
5	15	0.40 (0)	0.25 (0.050)
6	6	0.33	0.233
8	8	0.25	0.13
9	9	0.22	0.153
10	10	0.20	0.12
11	11	0.18	0.091
Mean component scores	--	0.86 (0.23)^	0.51 (0.21)^
Mean component scores (excluding dyads)	--	0.55 (0.18)^	0.34 (0.14)^

Note: ^ $p < 0.001$

CHAPTER V – DISCUSSION

5.1 Network-Based Risk Factors

The identification of novel risk factors associated with gonorrhea is of utmost importance in the face of evolving AMR against the last remaining clinically tested class of antibiotics available for treatment.[108] Despite the traditional identification of a number of risk factors associated with an increased risk of gonorrhea, the incidence continues to rise.[5,13] Specific to the region in which the data were gathered, novel, localized strategies are required to mitigate the current gonococcal burden evidenced by the recent surge in infection. A decrease in transmission limits the emergence and spread of AMR strains within the defined population. The current study utilized gonorrhea specific data from a PHU in Ontario, which permitted rapid access and analysis of the data necessary to address the recent increase in incidence. Sexual NA was integrated into the traditional epidemiological analysis of surveillance data with the objective of identifying the sexual relationship structure in the defined population while determining the risk factors influencing the position of an individual within the larger sexual network. All of which was conceptualized as a way to inform public health practice.

The research question of whether network-based risk factors are associated with gonococcal transmission was addressed from both the component (network structure) and individual (network position) network levels of measurement. Linear structures were identified as important reservoirs of gonococcal transmission while analysis of the individual network level revealed a significant association between network position, specifically a central position, and a positive gonorrhea status. A number of risk factors including anonymous sex, greater than one sexual partner in the past six months, sex with

the same sex, a greater number of total risk factors and younger age were significantly associated with a central network position.

5.1.1 Network Structure

Previous research has identified disconnected, small, linear, acyclic structures during endemic phases of STI transmission.[24-26,143,146] Similar to previous research, the sexual network structure of the current sample resulted in a lack of interconnectivity and abundance of smaller components. Additionally, a number of larger linear structures were observed, which aligns with previous gonococcal-NA.[24,25,162] The linear structures represented 50.00% of the components with four or more individuals, accounting for 62.50% of the gonococcal infections in larger components. A slightly lower proportion of radial structures (43.75%) were observed which accounted for 31.25% of the gonococcal infections. Although radial structures were observed and have less commonly been reported in gonococcal-networks,[25,26] a significant protective effect for individuals in components with increasing centralization (radial structures) was identified when compared with components with decreasing centralization (linear structures) in the current sample. Therefore, radial structures although observed, do not appear to have significantly contributed to the transmission of gonorrhea in the current study. Analysis from the entire network perspective identifies linear structures as representing 7.55% of all components accounting for 18.18% of the infections.

These findings suggest that linear structures were an important reservoir in the maintenance and spread of gonorrhea in the current study. Therefore, linear structures have been identified as a network-based risk factor where the odds of gonorrhea are

greater in individuals who are members of linear sexual network structures. The observed linear structures and the importance in the transmission of gonorrhea align with the previously ascertained role core groups have in the maintenance of STIs in a defined population.[53,55,89,128] Through sexual NA however, the structure of the core groups is analyzed which supports the development of effective prevention/control strategies. In the current study for example, a number of linear structures were observed which individually did not encompass a significant portion of the sample therefore, a targeted network-based prevention strategy would be ineffective.

Despite the similarities with previous sexual networks observed during endemic phases of infection, the identified cyclical structures combined with the significant underreporting of sexual partners suggests a larger network with greater interconnectivity existed in the sample at the time the data were gathered. Furthermore, the average component size of 3.6 was larger than the mean component size previously identified (mean range of 2.9 to 3.5) in contact tracing studies during endemic phases of gonorrhea.[24-26] Increasing component size and interconnectivity, however, did not significantly influence gonorrhea status in the current study. The lack of association with component size and interconnectivity, which has previously been reported,[153] is likely a result of the observed lack of sexual history reporting and the large proportion of smaller components.

In summary, the data do not suggest epidemic levels of gonorrhea were present in the sample during the defined time period since structures characteristic of epidemic/outbreak settings including very large, interconnected, primarily cyclical structures were not observed.[146,163] Nevertheless, the observed network structure may

represent infection transmission greater than that observed during disease equilibrium.[146] A definite conclusion however, cannot be ascertained in the current sample due to a lack of comparison with a network structure observed during confirmed endemic transmission in the defined population. Comparison with the network structure over a two-year period prior to the recent increase would aid in discerning whether the recent spike in gonococcal infections was a result of a greater number of diagnostic tests performed or a result of increased transmission.

5.1.2 Network Position

A central network position, determined by the composite variable incorporating degree and two-reach centrality, was significantly associated with a positive gonorrhea status. More specifically, individuals in the centre of components with complete centralization (radial structures) and the interior of non-radial structures were more likely to have a positive gonorrhea status compared with members of dyads and participants found on the periphery of components with greater than two individuals.

Network position was analyzed due to the significant association between individual measures of centrality and gonorrhea status. Additionally, the protective association between increased component centralization and gonorrhea status despite the presence of individuals with a positive gonorrhea status located in the center of the identified highly centralized structures (radial structures) prompted further investigation. Furthermore, comparison between participants stratified by network component size does not allow for the distinction in network position within components therefore, the novel technique developed by Fichtenberg and colleagues was used in the current study.[153,164]

The current method does not require the determination of an arbitrary cut-point of the remaining continuous measures of centrality (eigenvector, closeness and between centrality) in order to classify network position therefore, can be replicated in additional studies. The classification method however, was validated in the current study by comparing network position classification with the remaining measures of centrality.

Fichtenberg *et al.* reported a significant association between network position and infection status, which included both chlamydia and gonorrhea due to the limited number of gonorrhea cases.[153] Specifically, members of dyads were less likely to have gonorrhea compared with members found in the interior of components and individuals found on the periphery of components with greater than two individuals.[153] The current study supports the previously identified association between network position and infection status by conducting a similar analysis on an isolated gonococcal-network. As a result of the sample size in the current study, members on the periphery of components were combined with members of dyads and compared with members in the interior of components (radial and non-radial components). Central positions were significantly associated with a positive gonorrhea status however the distinction between members on the periphery and in dyads was not determined due to sample size limitations.

Demographic variables and risk factor reporting differed between central and non-central participants. In the current study, central members were more likely to be younger, have a greater number of reported risk factors, engage in anonymous sex, have more than one sexual contact in the last six months and have sex with the same sex. Variation in risk factors between network position was also determined by Fichtenberg and colleagues in a follow-up study investigating differences in SES between network position.[164] Poverty,

determined by the residence of the participant, was found to be statistically associated with network position. Central individuals were more likely to reside in the poorest third of the neighbourhoods.[164] The behavioural and demographic variables compared between individuals stratified by network position in the current study have not previously been investigated. The identified risk factors associated with a central network position will aid in identifying individuals with a greater odds of having gonorrhea.

Comparison between the abovementioned study and the current study is challenging due to the differences in the sampling methods used and the sample demographics. Fichtenberg *et al.* conducted a population-based sexual network study involving black adolescents in San Francisco and utilized the snowball sampling method.[153] Nonetheless, contact-tracing and snowball sampling employ a similar network sampling methodology where index participants are required to name their sexual partners in order to determine the network structure.[173] Furthermore, two-waves of snowball sampling was achieved in the population-based study which aligns with what was observed in the current contact-tracing based sample.[24] Previous comparison between the network structures observed in the adolescent population compared with studies with greater diversity in age and race/ethnicity resulted in similar findings, which may further support the ability to make comparisons between the current study and the population-based study.[24]

In summary, a recently developed method was used to identify sexual network-based risk factors associated with gonorrhea. The positive association between a central position and gonorrhea status represents an additional network-based risk factor, which will support the development of effective prevention/control strategies. Analysis of the

demographic and behavioural factors influencing network position further established risk factors associated with gonorrhea.

5.1.3 Partner mixing

Patterns of partner mixing have previously been identified as important risk factors associated with the transmission of gonorrhea.[22,32,54,81] Dissortative mixing, defined as variation in a risk attribute between sexual partners, has been found to increase the risk of gonorrhea.[22] Specific to age, previous research has identified an increased risk of gonorrhea in individuals who engage in sexual relationships with partners who differ in age.[32,81] Therefore, the observed assortative mixing with respect to age in the current study does not reflect high-risk partner mixing and likely did not contribute to the observed increase in the incidence of gonorrhea. Furthermore, the number of risk factors reported by participants in the current study did not influence partner selection. The lack of correlation suggests the variation in the number of risk factors between sexual partners was not a significant risk factor in the transmission of gonorrhea in the current study.

5.2 Data Quality

The data included in the current study were collected, entered and analyzed following rigorous data standards with the objective of providing an accurate overview of gonorrhea cases and named sexual partners in the defined region. The Data Standards and Reporting Subcommittee of the iPHIS Advisory Committee together with PHO and the MOHLTC have developed the iPHIS Risk Factor Guide to guide case investigation and data entry with the objective of supporting the collection of complete and consistent risk factor data.[166] Additionally, the mandatory fields included in iPHIS are entered using

form-fillable fields aimed at reducing data entry errors. Standardized reports developed by the local PHU are then used to clean the data. Prior to the analysis in the current study, the data was additionally cleaned and missing data removed.

The sexual network of the current sample includes cases of gonorrhea and the named sexual contacts of the index cases since public health procedures in Ontario do not mandate sexual contact identification for negative cases of gonorrhea.[174] Follow-up of the named sexual partners involves testing for gonorrhea, evaluation of risk factors and determination of sexual partners if the named contact tested positive for gonorrhea. Of the named sexual contacts with a confirmed gonorrhea status (n = 167, first wave-sampling), the majority (53.29%) did not reappear in the dataset as a laboratory confirmed or epidemiologically linked case. Nevertheless, detailed risk factor data was obtained from 48.31% (43 of the 89 contacts) of the named contacts that did not reappear in the dataset. Alternatively, a number of cases were subsequently named a contact (22.75% of all contacts) in which risk factor data was gathered from all individuals. Additionally, 23.95% (40 of the 167 contacts) of the contacts tested positive for gonorrhea and were identified as a case and risk factor data was available for 90% of the individuals. Therefore, the first wave of sampling included 167 named sexual contacts of which 78 (representing second wave-sampling) reappeared in the dataset as a case. In summary, risk factor data was obtained for 78.17% of individuals with a confirmed gonorrhea status. More specifically, risk factor data was available for 94.05% of cases and 70.06% of contacts.

Similarly, demographic information was obtained for 78.46% of cases and named sexual contacts in a sexual NA conducted in Manitoba, Canada derived from public

health data.[25] The study did not report whether demographic information was equally available for cases and contacts and the distinction between the number of cases and contacts was not provided.[25] De *et al.* conducted a sexual NA during an outbreak of gonorrhea where 107 index cases and 75 named sexual contacts were identified.[143] Similar to the study conducted in Manitoba, detailed description of case and contact reporting was not provided. Additional comparison of the current study with sexual network research involving population-based snowball sampling, revealed improved risk factor reporting and follow-up in the current study. Stoner *et al.* randomly selected study participants from STI clinics in Seattle, Washington resulting in the identification of 246 sexual partners in which 29.27% consented to participate.[14] Subsequently, 5.45% of the second wave of named sexual contacts consented to participate in the study.[14] Fichtenberg *et al.* conducted a population-based longitudinal study where two waves of contact tracing were performed where a slightly greater proportion (56.00%) of the named sexual contacts were interviewed.[24] The gonorrhea specific iPHIS data included in the current study resulted in greater follow-up with named sexual contacts compared with previous studies using both contact tracing and snowball sampling.

5.3 Strengths

5.3.1 Isolated Analysis of Gonococcal-Networks

The current study has built on previous research by analysing an isolated gonococcal-network. Conclusions drawn from the study are a reflection of the transmission of gonorrhea and are not influenced by the sexual network structure of additional STIs such as chlamydia. As a result of the common co-infection between gonorrhea and

chlamydia[175] in addition to a limited number of gonococcal cases, empirical network analysis has often combined the two STIs[24,32,146,153,164,176,177] limiting the number of studies focused solely on gonococcal-networks.[26,31,143,162] NA and disease transmission models have identified distinctive demographic, behavioural, network and transmission characteristics between individuals with gonorrhea and chlamydia therefore, independent analysis is necessary to further STI-specific understanding.[14,25,142,178]

Firstly, gonococcal- and chlamydial-network members have been found to differ demographically by race/ethnicity, education and unemployment status.[14] Additionally, gonococcal-network members have been reported to have a greater number of partners resulting in larger components.[14] As previously mentioned, linear structures are predominant in the transmission of gonorrhea compared with combined radial and linear structures observed with chlamydial transmission.[25] Disease transmission models evaluating the number of sexual partners required for gonorrhea and chlamydia maintenance within a population support the observed variation in network structure.

Brunham and Plummer evaluated disease transmission of gonorrhea and chlamydia using the R_0 of an infectious disease.[178] The R_0 of an infectious disease is a function of three components ($R_0 = \beta c D$) including the transmissibility of disease (β), contact rate between infected and susceptible individuals (c) and duration of infectivity (D). Constants of transmissibility of disease (β) and duration of infectivity (D) were established for both gonorrhea and chlamydia.[142] With these parameters in place, it was determined that an estimated four sexual partners/year are necessary for chlamydia to reach disease equilibrium (R_0=1) within a susceptible population whereas 13 sexual partners/year were required for gonorrhea to maintain the same infectious state.[178]

Therefore, radial components are more common in chlamydial infections because fewer sexual partners are required to maintain constant rates of chlamydial infection. The reduced number of positive gonorrhea cases observed in radial structures is also supported by the greater number of sexual partners required to maintain gonorrhea in a defined population. Individuals on the periphery of radial gonococcal-structures have a reduced number of sexual partners thereby reducing the likelihood of acquiring gonorrhea while members of non-radial components have a greater number of sexual partners and are more likely to acquire the infection.

5.3.2 Regional Analysis of Gonococcal-Networks

The geographic diversity of gonococcal-network research to date is limited. The recurring locations of empirical sexual network research include Colorado Springs (Colorado, US),[17,31,146] San Francisco (California, US),[24,153,164] Seattle (Washington, US),[14,32] Sheffield (South Yorkshire, UK),[26,162] London (UK),[162] Alberta (CAN)[143] and Manitoba (CAN)[25,176]. The current study has contributed to the limited number of empirical studies and has investigated a novel population in Ontario at a regional level. The advantages of investigating this population are two-fold. Firstly, previous findings such as the specific network structures observed in the transmission of gonorrhea are validated in a new population. Secondly, the application of NA at a regional level enables timely and focused analysis of gonorrhea cases and named sexual partners in a region currently faced with an increasing incidence of gonorrhea. Provincial data would not have improved the current study since regionally specific characteristics would be lost among the collated data from the 36 PHUs in Ontario. Furthermore, previously observed variation in

demographic characteristics and sexual behaviour between defined geographic regions warrants enhanced analysis of localized surveillance data.[6] Local analysis of surveillance data utilizing combined epidemiological and NA methodology provided an evaluation of the sexual network structure of the region in addition to regionally specific risk factors. Utilization of the data from the local PHU will also enable rapid knowledge translation, which can be used to inform prevention/control strategies for the PHU of the region under investigation.

5.3.3 Contact Tracing

The use of the gonorrhea-specific iPHIS data from the PHU provides the most comprehensive data available for gonorrhea cases and named sexual partners in the defined region. As a result of the mandated sexual partner reporting, the data are a rich source for sexual NA. Furthermore, the data do not include risk factor reporting for sexual contacts by the index case, which is a less reliable method used in previous research.[32] Follow-up of named sexual contacts improves the accuracy of the risk factors of named sexual contacts included in the analysis.

Additionally, limited communication between public health and research institutions in the past has reduced the use of contact tracing data in empirical research.[177] The development of a data sharing agreement between the academic institution and PHU for the current study has promoted ongoing investigation of valuable STI data in the future. The current study has demonstrated the usefulness of utilizing iPHIS data to analyze gonococcal-networks and associated risk factors while identifying areas requiring improvement.

5.4 Limitations

5.4.1 Passive Surveillance Data

As previously mentioned, the provincially mandated contact tracing involves the identification of gonorrhea cases and their named sexual contacts within 60 days of symptom onset. The nature of the data collection creates limitations inherent to sexual network research derived from passive surveillance data such as the iPHIS data. Firstly, initial identification of network members during sexual NA is restricted to infected cases. Therefore, the resulting sample was dependent on contact referrals of confirmed cases and does not reflect the sexual network structure of a random sample of the defined population. Previous research however, has concluded that sexual NA where index cases were identified individuals with gonorrhea, improves the prediction of transmission compared with network patterns identified through a random sample of the population.[29] The lack of representation of marginalized individuals from a population-based sample hinders the prediction of STI transmission since specific risk factors of marginalized populations are significantly associated with STI risk.[29] Nevertheless, a coupled analysis using both methods provides a comprehensive understanding of the sexual networks in a defined population.

Additionally, named contacts that do not reside in the region represented by the local PHU are not included in the region specific database. In the current study however, only one named sexual partner was referred to another PHU according to the public health nurse contact status reporting. Moreover, sexual networks are strongly influenced by the number of contact tracing waves included in the data. The number of waves in the current study was determined by the infection status of the named sexual contacts.

Contact tracing was terminated in situations where a sexual partner was named who did not test positive for gonorrhea or was lost to follow-up. Consequently, identified components in the study may appear to be smaller and less interconnected.

5.4.2 Sexual Network Research

A number of limitations are inherent to sexual network research despite the sampling method used. Sexual NA findings derived from both surveillance and survey/interview data obtained in clinical and research settings, respectively, are biased as a result of underreporting of sexual contacts.[22] Incomplete representation of the sexual relationships underestimates network size and reduces the accuracy of research findings. Underreporting is influenced by an individual's reluctance to name all sexual partners, hesitance to provide adequate contact information for locating partners and inability to provide information regarding anonymous sexual partners.[22] Furthermore, sexual contact names and required locatable information are often obtained yet individuals may be difficult to reach.[22]

Although difficult to eliminate, case management and legislation in Ontario has been established in order to limit underreporting and reduce public risk. According to the Case Management of *N. gonorrhoeae* policy developed by the PHU of the region under investigation, a public health nurse must contact sexual partners within two business days of case identification. Sexual partners are contacted through the most appropriate method including phone calls at varying times/days, text messaging, email, facebook contact, letter or a home visit. Four attempts are made to reach the named sexual contact through a variety of methods within a two-week period. Following the two-week period a stern

letter is sent. Failure to contact the sexual partner within three weeks requires specific case management by the Sexual Program manager. Additionally, when there is reason to believe an identified case is not being truthful or is withholding information about their sexual contacts, public health has the power under section 22 of the HPPA to order an individual to disclose this information.[96] Nevertheless, a significant lack of sexual partner reporting was observed in the current study, which may have led to an underestimation of the size and interconnectivity of the observed sexual network. Additionally, 69 isolates were identified and excluded from analysis since they represent participants with confirmed gonorrhea with incomplete sexual histories who were not named as sexual contacts. The position of isolates within the larger network remains unknown. Lastly, risk factor data is reflective of self-reporting. An individual may not accurately disclose their sexual history and behaviour, which limits the identification of risk factors associated with network position.

Despite the observed limitations, the current study included the most comprehensive gonorrhea case and contact data available for the region under investigation. The data provided a necessary portrait of the sexual partnership patterns in the region while identifying novel risk factors. Furthermore, empirical research despite the associated limitations is required to build on the limited number of studies which have analyzed the patterns of sexual relationships of specific STIs.[24]

5.5 Implications

The OPHS outline the minimum requirements of program delivery for public health programs across Ontario, which include assessment and surveillance, health promotion

and policy development, disease and injury prevention and health protection.[179] In brief, the requirements specific to STIs involve ongoing surveillance followed by epidemiological analysis of trends over time, emerging trends and priority populations.[179] The requirements were established with the objective of achieving timely identification of cases and associated risk factors, which are then used to effectively meet the requirements set out by the OPHS.[179] The understanding of STI transmission has been enhanced as a result of the integration of sexual NA within traditional epidemiological methods in previous research in addition to the current study.[22,146,153,177] Therefore, sexual NA should be considered as an addition to the current analysis of surveillance data used by the PHU included in the study in order to improve health promotion and STI prevention. Prior to the incorporation of sexual NA within PHUs across Ontario, representing diverse populations, future research is required (see section 5.6 Future Directions).

5.5.1 Surveillance

Evaluating the usefulness of NA as a novel technique used to analyze surveillance data resulted in a number of benefits. In the current sample, sexual NA provided a rapid means of describing trends in gonococcal incidence while identifying network-based risk factors associated with gonorrhea. The identified risk factors would not have been considered during traditional epidemiological analysis.

Membership in linear structures in addition to the position of an individual within a component was found to be significantly associated with a positive gonorrhea status. Of the individuals in high-risk central positions, 25.49% would not have been identified if

NA was not performed. That is, the use of self-reported sexual contacts as a method of identifying network position does not accurately identify all central participants. Although the association between central position and gonorrhea may seem predictable, the importance lies in the ability to identify high-risk central individuals and the associated risk factors. Furthermore, the abovementioned results combined with a visual analysis of the network structure do not suggest a super-spreader was responsible for contributing a disproportionately large amount to the transmission of gonorrhea. Additional noteworthy surveillance findings include the observed underreporting of sexual partners and abundance of smaller components, primarily dyads and triads.

In summary, the findings of the current study enhance the understanding of gonococcal transmission in the defined region, which supports the development of strategies aimed at reducing the spread of gonorrhea. The specific focus on gonorrhea despite chlamydia being the most common reportable STI,[5,12] is necessary due to the evolving gonococcal resistance against ESCs (i.e., the remaining reliable antibiotic class available for treatment).[8,9,104,119] The observed treatment failures in cases of gonorrhea treated with cefixime combined with trends in decreasing susceptibility to ceftriaxone in Ontario,[12,97] emphasizes the urgency in reducing the incidence of gonorrhea in all regions of the province. PHUs maintain a crucial role in preventing the emergence and transmission of ESC resistant strains.[180] The public health response requires efforts to reduce the incidence of gonorrhea through health promotion, screening and partner treatment.[180] The network-based risk factors observed in the current sample provide a new perspective on gonococcal transmission, which should be considered in the planning of prevention/control strategies.

5.5.2 Prevention and Disease Control Strategies

Sexual NA, employed as a novel method of analyzing surveillance data, has the potential to facilitate the selection of the most appropriate prevention/control strategies aimed at reducing the spread of gonorrhea in the region under investigation. Firstly, the identification of a number of linear structures as important reservoirs of gonococcal transmission in addition to a large number of smaller components suggests a targeted high-risk aggregate approach would not reach a significant proportion of the population. Where groups of individuals are identified by membership in a common component.[181] Alternatively, the presence of large, highly interconnected structures including large proportions of the entire sample would warrant an aggregate approach. Population-based primary prevention focused on behavioural interventions would better target the identified sexual network structure of the defined region.

In addition to primary prevention, secondary prevention focused on early detection and treatment efforts is required to reduce the transmission of gonorrhea. STI screening focused on risk factors significantly associated with central positions would promote early detection of gonorrhea in high-risk individuals identified through NA. The identified risk factors include younger individuals who report a number of risk factors with particular attention to anonymous sex, multiple sex partners in the past six months and who have sex with the same sex. Combining the newly identified risk factors with risk factors previously determined to be associated with a positive gonorrhea status incorporates both traditional and novel identification of high-risk individuals.

Partner treatment strategies are also an important public health secondary prevention strategy, which involves expedited treatment or standard referral.[182] With

expedited treatment, index cases are given medication to provide to their sexual partners whereas standard referral involves advising partners to seek medical attention. Previous research has demonstrated improved success of gonococcal control through expedited treatment.[182,183] The success of expedited treatment is dependent on the ability of an individual with gonorrhea to identify both previous and current sexual partners.[182] In the current study, it is unclear whether the observed lack of sexual partner reporting is a result of deliberate withholding of information or due to an inability to provide information regarding anonymous sexual partners. Independent analysis of the isolates suggests a large proportion of these individuals were unable to identify sexual contacts since 43.75% reported anonymous sex, 20.31% experienced judgment impaired by alcohol or drugs during sexual activity, 4.69% were sex trade workers and 3.13% had sex with a sex trade worker. Analysis of individuals in components with two or more individuals does not provide as definitive of an explanation. The proportion of individuals reporting anonymous sex (22.48%), judgment impaired by alcohol or drugs during sexual activity (3.46%), being a sex trade work (3.46%) and having sex with a sex trade worker (2.80%) was lower when compared with isolates.

In the current population, improved interviewing techniques would help determine whether the lack of sexual history reporting is a result of reluctance to name sexual partners or inability to provide contact information.[182] The inclusion of an assessment of how a patient responded when asked about their sexual history within the mandatory fields in iPHIS would aid in identifying the cause of poor sexual history reporting. The public health nurse would be able to document whether the case displayed reluctance or an inability to provide sexual contact information. Enhanced awareness of

trends in sexual contact reporting would aid in determining whether expedited treatment would be effective in the given population. Furthermore, as per the Sexually Transmitted Infection Case Management and Contact Tracing Best Practice Recommendations, strategies of addressing reluctant cases (e.g. assurance of confidentiality, reinforcing the severity of the infection and risk of re-infection) should be enforced with the objective of improving contact reporting.[174] Additionally, sexual NA would serve as a useful method of identifying the network position of resistant cases of gonorrhea within a defined sexual network. The ability to accurately identify the position of resistant cases and their sexual partners would enable rapid treatment of the index cases in addition to contacts and reduce the transmission within the larger network.

Lastly, sexual NA is required to accurately identify the network structure and position of an individual (central vs. non-central) within a larger sexual network. Following the identification of network structure, individuals in linear structures and central positions who were not followed-up by a public health nurse should be a primary focus due to the previously identified association with a positive gonorrhea status.

5.5.3 Integrated Public Health Information System

The results of the current study have helped highlight gaps in risk factor identification using the iPHIS data. The collected demographic and risk factor data included in the study were limited by the previously established mandatory reporting fields found in iPHIS. Specific risk factors previously found to be significantly associated with gonorrhea including race/ethnicity and SES were not included in the data obtained from the iPHIS.[51,53,54,57-61,143] Including the aforementioned risk factors in iPHIS would

improve the understanding of the sexual networks and risk factors associated with gonorrhea.

5.6 Future Directions

The application of NA in the current region was the first attempt at enhancing the understanding of sexual networks within the defined population. As a result of the novelty of sexual NA as a method of analyzing surveillance data, additional research is required to validate the current findings. A population-based random sampling approach will strengthen the understanding of the patterns of sexual relationships within the defined region. Comparison between network structures and high-risk network positions is required to support the findings of the current study.

Despite the usefulness of the rich data gathered through iPHIS, expanding the current mandatory fields will maximize the understanding of high-risk populations. The addition of the risk factors, which are not currently included in the iPHIS, will improve the risk-factor analysis of high-risk populations. Furthermore, the inclusion of a field within the iPHIS identifying the cause of a lack of sexual history disclosure will provide guidance for the implementation of the most efficient partner treatment strategy. Piloting NA as a method of analyzing surveillance data in PHUs across Ontario using the expanded iPHIS database will provide an understanding of the usefulness of the novel method in regions with varying population sizes and demographics. Sexual NA can also be employed as a useful evaluation method following the implementation of prevention/control strategies.

The results of the study in addition to the public health implications will be summarized and reported to the potential users of sexual NA (e.g. data analysts, sexual health promoters), program managers and policy makers of the PHU in which the data were gathered. Effective knowledge translation of the evidence-based findings will influence the inclusion of sexual NA in the education of public health professionals, which in turn will influence analysis of local surveillance data using sexual NA. The integration of sexual NA knowledge and skills within public health practice has the potential to strengthen the understanding of gonococcal transmission and will support the development of effective prevention/control strategies.

CHAPTER VI – CONCLUSION

In the current study, a significant association between network-based risk factors and a positive gonorrhea status was revealed following a sexual NA of a defined region in Ontario experiencing an increase in the incidence of gonorrhea. Network-based risk factors at both the component (network structure) and individual (network position) levels of measurement were identified. Consistent with previous research, linear structures were important reservoirs of gonococcal transmission, which identifies an increased risk of gonorrhea in linear components compared with radial structures. Analysis of the individual network level identified a significant association between a central network position and a positive gonorrhea status. Although the association between network position and gonorrhea status is predictable, the importance lies in the successful identification of high-risk individuals. The use of self-reported sexual contacts as a method of identifying network position does not accurately identify all central participants. Moreover, a number of risk factors were significantly associated with a central position including anonymous sex, greater than one sexual partner in the past six months, sex with the same sex, a greater number of total risk factors and younger age.

The increasing incidence of gonorrhea in Canada coupled with evolving AMR against the last remaining, clinically tested class of antibiotics available for treatment underscores the importance of identifying novel risk factors. The network-based risk factors identified through sexual NA facilitates the selection of appropriate prevention and disease control strategies aimed at reducing the transmission of gonorrhea. Furthermore, the results of the current study have highlighted gaps in risk factor identification by PHUs using the iPHIS. Integration of the identified risk factors will

enhance risk-factor analysis of high-risk individuals in the defined region. Future research aimed at assessing the success of sexual NA as a method of analyzing surveillance data in various populations will aid in determining whether including sexual NA as core competency for public health professionals is warranted.

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APPENDIX A - Pathogenesis of Gonococcal Infections

Gram-negative bacteria commonly possess long filamentous appendages extending from their outer membrane known as pili.[33] Pili and the protein subunits known as pilins, are crucial virulence factors required for colonization of host tissue.[33] Pili are categorized into four groups depending on how they are assembled. Type IV pili, formed by pilin polymerization, are found on the outer membrane of *N. gonorrhoeae*.[34] The pilus fiber of *N. gonorrhoeae* is primarily composed of the major pilin subunit PilE and has the pilin protein PilC located on the tip of the appendage.[33] Gonococcal pili mediate initial host cell adhesion and challenge the difficulties faced during host cell attachment and colonization.[33,34] The pili overcome charge repulsion created by the negative charge of both the bacterium and host cell. The appendages, which do not carry the negative charge, provide sufficient distance from the host cell for adhesion to occur without repulsion.[33] PilC is an adhesive factor essential for host cell receptor recognition and binding.[33] PilE has recently been shown to assist in receptor recognition, further promoting bacteria and cell interaction leading to infection.[35] A number of proteins found on non-ciliated epithelial host cells serve as receptors for gonococcal pili including the complementary regulatory protein CD46 found on all nucleated cells, the human complement regulatory C4B-binding protein and the complement regulatory protein 3.[33,35,37] Phase and antigenic variation in pilins results in the assembly of gonococcal pili with altered binding properties and the ability to target various human host tissues.[34,35]

Opacity proteins also contribute to cell adhesion and gonococcal tropism through binding with specific host cell surface proteins.[1] Opacity proteins are divided into two classes based on their affinity for either members of the human carcinooembryonic antigen-related cellular adhesion molecule family or heparin sulfate proteoglycans.[1] The ability of opacity proteins to respond to changes in the female reproductive tract by developing variant phenotypes best suited for the stages of the menses cycle provides another example of the successful adaptive mechanisms exhibited by *N. gonorrhoeae*.[37]

APPENDIX B – Gonococcal Risk Factors included in the iPHIS

Behavioural/Social Factors
Anonymous sex
Condom breakage
Consumed breast milk
Contact is HIV positive
Contact lived in or visited a country where HIV is endemic (specify country)
Contact visiting from outside province (specify province or country)
Fighting, biting, torture, blood brother
Inhalation drug use
Injection drug use
Judgment impaired by alcohol/drugs (specify)
Met contact through internet (specify)
More than one sex contact in last 6 months (specify approximate number)
New contact in past 2 months
No condom used
Other (specify)
Serosorting
Sex for drugs/shelter/food/survival
Sex trade worker
Sex with opposite sex
Sex with same sex
Sex with sex trade worker
Sex with transgender
Shared other drug equipment
Shared needles
Shared sex toys
Strategic Positioning

Medical Risk Factors
Client born to a case or carrier
Co-diagnosis/co-infection with existing STI (specify)
HIV status
Invasive surgical/dental/ocular procedures abroad (specify country & when)
Invasive surgical/dental/ocular procedures in Canada (specify when & where)
Organ/tissue transplant (specify when & where)
Organ/tissue transplant abroad (specify country & when)
Other (specify)
Pregnant
Received blood or blood products (specify when & where)
Received blood or blood products abroad (specify country & when)
Repeat STI

Exposure Settings
Bath house
Blood exposure through shared accident
Correctional facility
Encounter following major event (specify)
Electrolysis and acupuncture
Occupational exposure to potentially HIV contaminated blood body fluids
Other (specify)
Other personal services
Other social venue (specify)
Tattoo and piercing
Travel outside province (specify province or country)
Travel to or live in a country where HIV is endemic (specify country)
Underhoused/homeless

APPENDIX C – Detailed Participant Result Summaries

Table C.1.1 Participant Gonorrhea Encounter Characteristics

Frequency (%)	Total	Isolates	Dyads	Triads	C *n*=4	C *n*=5	C *n*=6	C *n*=8	C *n*=9	C *n*=10	C *n*=11
Gonorrhea Encounter	*n =356*	*n=69*	*n=148*	*n=48*	*n*=32	*n=15*	*n=6*	*n=8*	*n=9*	*n=10*	*n=11*
Gonorrhea Status											
Confirmed Positive	234 (65.73)	69 (100.00)	91 (61.49)	26 (54.17)	20 (62.50)	10 (66.67)	4 (66.67)	1 (12.50)	7 (77.78)	4 (40.00)	2 (18.18)
Confirmed Negative	87 (24.44)	-	38 (25.68)	17 (35.42)	8 (25.00)	4 (26.67)	2 (33.33)	6 (75.00)	-	6 (60.00)	6 (54.55)
Undetermined	35 (0.83)	-	19 (12.84)	5 (10.42)	4 (12.50)	1 (6.67)	-	1 (12.50)	2 (2.22)	-	3 (27.27)
Multiple Gonococcal Infections											
>1 Gonococcal Infection	14 (3.93)	2 (2.90)	5 (3.36)	1 (2.13)	2 (6.25)	2 (13.33)	1 (16.67)	-	1 (11.11)	-	-
Date of Infection/Sexual Relationship											
2013	144 (40.56)	28 (40.58)	57 (38.51)	23 (48.94)	12 (37.50)	7 (46.67)	1 (16.67)	8 (100.00)	-	8 (80.00)	-
2014	207 (58.15)	40 (57.97)	91 (61.49)	25 (52.08)	20 (62.50)	7 (46.67)	3 (50.00)	-	8 (88.89)	2 (20.00)	11
13/14	5 (1.40)	1 (1.45)	-	-	-	1 (6.67)	2 (33.33)	-	1 (11.11)	-	(100.00) -
Detailed Encounter Type											
Case	153 (42.98)	69 (100.00)	61 (40.94)	12 (25.53)	4 (12.50)	1 (6.67)	2 (33.33)	1 (12.50)	1 (11.11)	1 (10.00)	1 (9.09)
Contact	124 (34.83)	-	57 (38.51)	22 (45.83)	13 (40.63)	5 (33.33)	2 (33.33)	7 (87.50)	3 (33.33)	6 (60.00)	9 (81.82)
Case subsequently named a contact	38 (10.67)	-	17 (11.49)	5 (10.42)	8 (25.00)	4 (26.67)	-	-	3 (33.33)	1(10.00)	-
Contact subsequently named a case	40 (11.24)	-	13 (8.78)	9 (18.75)	7 (21.88)	5 (33.33)	1 (16.67)	-	2 (22.22)	2 (20.00)	1 (9.09)
Case & Contact at two time points	1 (0.28)		-	-	-	-	1 (16.67)	-	-	-	-
Encounter Type											
Case	191 (53.65)	69 (100.00)	77 (52.03)	17 (36.17)	12 (37.50)	5 (33.33)	2 (33.33)	1 (12.50)	4 (44.44)	2 (20.00)	1 (9.09)
Contact	164 (46.07)	-	71 (47.97)	31 (64.58)	20 (62.50)	10 (66.67)	3 (50.00)	7 (87.50)	5 (55.56)	8 (80.00)	10 (90.91)
Case & Contact at two unique time points	1 (0.28)	-	-	-	-	-	1 (16.67)	-	-	-	-

Note: Varying sample sizes are a result of missing data
C = Component

Table C.1.2 Participant Demographic and Risk Factor Characteristics

	Total *n =321*	Isolates *n=69*	Dyads *n=129*	Triads *n=43*	C *n*=4 *n*=28	C *n*=5 *n=14*	C *n*=6 *n=6*	C *n*=8 *n=7*	C *n*=9 *n=7*	C *n*=10 *n=10*	C *n*=11 *n=8*
Demographics											
Age (years)(SD)	26.92 (10.64)	29.55 (11.45)	28.44 (11.80)	24.79 (6.13)	27.47 (11.10)	22.90 (5.44)	21.88 (7.26)	22.96 (4.12)	19.49 (2.58)	18.82 (1.22)	16.87 (1.52)
Gender											
Male	193 (60.12)	49 (71.01)	70 (54.26)	25 (58.14)	17 (60.71)	10 (71.43)	3 (50.00)	6 (85.71)	3 (42.86)	3 (30.00)	7 (87.50)
Female	128 (39.88)	20 (28.99)	59 (45.74)	18 (41.86)	11 (39.29)	4 (28.57)	3 (50.00)	1 (14.29)	4 (57.14)	7 (70.00)	1 (12.50)
Risk Factors	*n=261*	*n=64*	*n=104*	*n=33*	*n=23*	*n=12*	*n=5*	*n=1*	*n=5*	*n=6*	*n=8*
Risk Factor Data *Available*	261 (81.31)	64 (92.75)	104 (80.62)	33 (76.74)	23 (82.14)	12 (85.71)	5 (83.33)	1 (14.29)	5 (71.43)	6 (60.00)	8 (100.00)
RF Group											
Behaviour/Social(BS)	212 (81.23)	49 (76.56)	83 (79.81)	29 (87.88)	20 (86.96))	10 (83.33)	3 (60.0)	1 (100.00)	4 (80.00)	5 (83.33)	8 (80.00)
Medical (M)	4 (1.53)	3 (4.69)	-	-	-	1 (8.33)	-	-	-	-	-
BS & M	39 (14.94)	8 (12.50)	19 (18.27)	4 (12.12)	3 (13.04)	1 (8.33)	2 (40.00)	-	1 (20.00)	1 (16.67)	-
BS & E	3 (1.15)	2 (3.13)	1 (0.96)	-	-	-	-	-	-	-	-
BS, M & E	3 (1.15)	2 (3.13)	1 (0.96)	-	-	-	-	-	-	-	-
Total RFs (SD)	3.05 (1.60)	3.61 (1.88)	2.69 (1.35)	3.09 (1.72)	3.22 (1.20)	2.92 (1.44)	4.60 (0.89)	6.00 (0)	3.00 (1.22)	3.33 (0.74)	1.38 (0.74)
Reported Risk											
Sex with same sex	35 (13.41)	11 (17.19)	9 (8.65)	4 (12.12)	6 (26.09)	5 (41.67)	-	-	-	-	-
Anonymous sex	42 (16.09)	28 (43.75)	4 (3.85)	4 (12.12)	2 (8.70)	1 (8.33)	1 (20.00)	1 (100.00)	-	1 (16.67)	-
Condom breakage	11 (4.21)	4 (6.25)	2 (1.92)	2 (6.06)	-	1 (8.33)	1 (20.00)	-	-	1 (16.67)	-
>1 sex contact in the last 6 months	77 (29.50)	13 (20.31)	24 (23.08)	14 (42.42)	12 (52.17)	4 (33.33)	4 (80.00)	1 (100.00)	2 (40.00)	2 (33.33)	1 (12.50)
New contact in part two months	121 (46.36)	35 (54.69)	41 (39.42)	16 (48.48)	13 (56.52)	5 (41.67)	4 (80.00)	1 (100.00)	2 (40.00)	3 (50.00)	1 (12.50)
Lack of condom use	230 (88.12)	54 (84.38)	94 (90.38)	28 (84.85)	22 (95.65)	10 (83.33)	5 (100.00)	1 (100.00)	5 (100.00)	6 (100.00)	5 (62.50)
Sex with opposite sex	169 (64.75)	38 (59.38)	71 (68.27)	24 (72.73)	13 (56.52)	4 (33.33)	5 (100.00)	1 (100.00)	4 (80.00)	5 (83.33)	5 (50.00)
Judgment impaired by alcohol/drugs	16 (6.13)	13 (20.31)	2 (1.92)	1 (3.03)	-	-	-	-	-	-	-
Sex trade worker	6 (2.30)	3 (4.69)	1 (0.96)	1 (3.03)	-	-	1 (20.00)	-	-	-	-

Sex with a sex trade worker	4 (1.53)	2 (3.13)	1 (0.96)	1 (3.03)	-	-	-	-	-	-	-
Repeat Infection	46 (17.62)	13 (20.31)	19 (18.27)	4 (12.12)	3 (13.04)	3 (25.00)	2 (40.00)	-	1 (20.00)	1 (16.67)	8 (10.00)
Co-infection with Existing STI	3 (1.15)	3 (4.69)	-	-	-	-	-	-	-	-	-
HIV positive	2 (0.77)	2 (3.13)	-	-	-	-	-	-	-	-	-
Contact is HIV positive	3 (1.15)	-	1 (0.97)	-	1 (4.35)	-	-	-	1 (20.00)	-	-
Travel outside of province	3 (1.15)	1 (1.56)	2 (1.92)	-	-	-	-	-	-	-	-
Contact visiting outside of province	1 (0.38)	-	-	-	-	-	-	1 (100.00)	-	-	-
Met contact through the internet	11 (4.21)	5 (7.81)	3 (2.88)	2 (6.06)	-	1 (8.33)	-	-	-	-	-
Pregnant	4 (1.53)	1 (5.56)	3 (2.88)	-	-	-	-	-	-	-	-
Bath House	1 (0.38)	1 (1.56)	-	-	-	-	-	-	-	-	-
Sex Toys	1 (0.38)	1 (1.56)	-	-	-	-	-	-	-	-	-
Homeless	2 (0.77)	2 (3.13)	-	-	-	-	-	-	-	-	-

Note: Individuals without a confirmed gonorrhea status were excluded

Table C.2.1 Network Structure

Component Size	Topology	No. of Individuals (*n*)	Frequency of Components (*n*)	Density (SD)	Diameter (SD)	Degree Centralization (SD)^	Closeness Centralization (SD)^	Betweenness Centralization (SD)^	Eigenvector Centralization (SD)^	K cores, where k=2
2	--	148	74	1.00 (0)	1 (0)	--	--	--	--	--
3	*See Table 3.2*	48	16	0. 69 (0.083)	1.94 (0.25)	0.94 (0.25)	0.94 (0.25)	0.94 (0.25)	0.94 (0.25)	1 (*Clique*)
4	*See Table 3.2*	32	8	0.52 (0.059)	2.38 (0.52)	0.71 (0.33)	0.75 (0.29)	0.75 (0.28)	0.76 (0.25)	1 (*Clique*)
5	*See Table 3.2*	15	3	0.40 (0)	3.33 (0.58)	0.44 (0.24)	0.56 (0.13)	0.61 (0.17)	0.71 (0.16)	0
6	T-Shape	6	1	0.33	4	0.4	0.56	0.64	0.75	0
8	Radial	8	1	0.25	2	1.00	1.00	1.00	1.00	0
9	Branching linear	9	1	0.22	5	0.20	0.36	0.53	0.57	0
10	Branching Radial	10	1	0.20	4	0.72	0.76	0.90	0.97	0
11	Radial	11	1	0.18	2	1.00	1.00	1.00	1.00	0
Mean component scores		--	--	0.86 (0.23)	1.42 (0.79)	--	--	--	--	--
Mean component scores (excluding dyads)		--	--	0.55 (0.18)	2.41 (0.84)	0.79 (0.32)	0.82 (0.28)	0.84 (0.26)	0.86 (0.24)	--
r_s† (*p*-value)		--	--	-0.98 (<.0001)	0.97 (<.0001)	-0.52 (0.0021)	-0.51 (0.0025)	-0.50 (0.0033)	-0.49 (0.0046)	--

Note: ^Not calculated for dyads

† Spearman rank correlation coefficient with component size

Table C.2.2 Network Structure Stratified by Component Topology

Component Size	Frequency of Components (*n*)	Density (SD)	Diameter (SD)	Degree Centralization (SD)	Closeness Centralization (SD)	Betweenness Centralization (SD)	Eigenvector Centralization (SD)	K cores, where k=2
3 (Overall)	16	0. 69 (0.083)	1.94 (0.25)	0.94 (0.25)	0.94 (0.25)	0.94 (0.25)	0.94 (0.25)	1 (*Clique*)
3 (Linear)	15	0.67 (0)	2.00 (0)	1.00 (0)	1.00 (0)	1.00 (0)	1.00 (0)	0
3 (Cyclical)	1	1.00	1.00 (0)	0	0	0	0	1
4 (Overall)	8	0.52 (0.059)	2.38 (0.52)	0.71 (0.33)	0.75 (0.29)	0.75 (0.28)	0.76 (0.25)	1 (*Clique*)
4 (Linear)	3	0.50 (0)	3.00 (00	0.33 (0)	0.42 (0)	0.44 (0)	0.51 (0)	0
4 (Radial)	4	0.5 (0)	2.00 (0)	1.00 (0)	1.00 (0)	1.00 (0)	1.00 (0)	0
4 (Cyclical)	1	0.67	2.00 (0)	0.67	0.75	0.67	0.57	1
5 (Overall)	3	0.40 (0)	3.33 (0.58)	0.44 (0.24)	0.56 (0.13)	0.61 (0.17)	0.71 (0.16)	0
5 (Linear)	1	0.4	4.00	0.17	0.42	0.42	0.52	0
5 (Branching Linear)	2	0.4 (0)	3.00 (0)	0.58	0.64 (0)	0.71 (0)	0.80 (0)	0

Table C.3.1 Network Centrality

Component Size	Topology	No. of Individuals	Frequency of Components (n)	Degree Centrality (SD)	Normalized Degree Centrality (SD)^	Two-reach Centrality (SD)	Normalized Closeness Centrality (SD)^	Normalized Betweenness Centrality (SD)^	Normalized Eigenvector Centrality (SD)^
2	--	129	74	1.00 (0)	--	0.00 (0)	--	--	--
3	*See Table 4.2*	43	16	1.42 (0.50)	0.71 (0.25)	0.58 (0.50)	0.81 (0.17)	0.35 (0.48)	0.82 (0.14)
4	*See Table 4.2*	28	8	1.64 (0.78)	0.55 (0.26)	1.21 (0.74)	0.70 (0.17)	0.31 (0.40)	0.70 (0.18)
5	*See Table 4.2*	14	3	1.57 (0.76)	0.39 (0.19)	1.57 (0.65)	0.57 (0.14)	0.31 (0.340	0.61 (0.20)
6	Branching Linear	6	1	1.67 (0.82)	0.33 (0.16)	1.67 (0.52)	0.51 (0.13)	0.27 (0.33)	0.54 (0.22)
8	Radial	7	1	1.86 (2.27)	0.27 (0.32)	5.14 (2.27)	0.60 (0.17)	0.14 (0.38)	0.47 (0.24)
9	Branching linear	7	1	2.00 (0.82)	0.25 (0.10)	2.14 (1.07)	0.41 (0.089)	0.32 (0.27)	0.49 (0.19)
10	Branching Radial	10	1	1.80 (1.87)	0.20 (0.21)	4.60 (2.27)	0.50 (0.13)	0.14 (0.30)	0.39 (0.23)
11	Radial	8	1	2.13 (3.18)	0.21 (0.32)	8.75 (3.54)	0.59 (0.17)	0.13 (0.35)	0.40 (0.24)
r_s† (*p*-value)	--	--	--	0.43 (<.0001)	-0.88 (<.0001)	0.88 (<.0001)	-0.67 (<.0001)	-0.10 (0.23)	-0.68 (<.0001)
Mean Individual Scores (*with dyads*)	--	252	106	1.31 (0.91)	--	1.02 (2.08)	--	--	--
Mean Individual Scores (*without dyads*)	--	123	32	1.63 (1.22)	0.49 (0.31)	2.10 (2.58)	0.67 (0.20)	0.27 (0.40)	0.65 (0.24)

Note: Individuals without a confirmed gonorrhea status were excluded

^Not calculated for members of dyads

† Spearman rank correlation coefficient with component size

Table C.3.2 Network Centrality Stratified by Component Topology

Component Size	No. of Individuals	Frequency of Components (n)	Degree Centrality (SD)	Normalized Degree Centrality (SD)	Two-reach Centrality (SD)	Normalized Closeness Centrality (SD)	Normalized Betweenness Centrality (SD)	Normalized Eigenvector Centrality (SD)
3	43	16	1.42 (0.50)	0.71 (0.25)	0.58 (0.50)	0.81 (0.17)	0.35 (0.48)	0.82 (0.14)
3 (Linear)	40	15	1.38 (0.49)	0.69 (0.25)	0.63 (0.49)	0.79 (0.16)	0.38 (0.49)	0.82 (0.14)
3 (Cyclical)	3	1	2.00 (0)	1.00 (0)	0 (0)	1.00 (0)	0.00 (0)	0.82 (0)
4	28	8	1.64 (0.78)	0.55 (0.26)	1.21 (0.74)	0.70 (0.17)	0.31 (0.40)	0.70 (0.18)
4 (Linear)	10	3	1.6 (0.52)	0.53 (0.17)	1.00 (0)	0.65 (0.13)	0.40 (0.34)	0.72 (0.17)
4 (Radial)	14	4	1.57 (0.94)	0.52 (0.31)	1.43 (0.94)	0.71 (0.19)	0.29 (0.47)	0.70 (0.20)
4 (Cyclical)	4	1	2.00 (0.82)	0.67 (0.27)	1.00 (0.82)	0.78 (0.17)	0.17 (0.33)	0.69 (0.20)
5	14	3	1.57 (0.76)	0.39 (0.19)	1.57 (0.65)	0.57 (0.14)	0.31 (0.340	0.61 (0.20)
5 (Linear)	5	1	1.40 (0.55)	0.35 (0.14)	1.20 (0.45)	0.52 (0.12)	0.33 (0.31)	0.61 (0.19)
5 (Branching Linear)	9	2	1.67 (0.87)	0.42 (0.22)	1.78 (0.67)	0.59 (0.14)	0.30 (0.37)	0.61 (0.21)

Note: Individuals without a confirmed gonorrhea status were excluded

APPENDIX D – Glossary of Terms

Component
A subgraph describes a group of individuals who are connected directly or indirectly with one another. More specifically, subgraphs involving two or three individuals are referred to as dyads and triads, respectively, and a subgraph with greater than three individuals is termed a component. To ensure consistency, the term component will be used regardless of size and when needed the number of individuals involved in the component will be stated.

Undirected (Symmetric) Component
An undirected component does not specify the direction of the relationship (i.e., the component does not incorporate who listed who as a sexual contact and whether the naming was reciprocated). In a directed (asymmetric) component the directions of the relationships are specified.

Adjacency Matrix
An adjacency matrix represents a component as a matrix including an identical list of nodes in both the rows (*i*) and columns (*j*). In an undirected adjacency matrix the bottom left and top right of the matrix, divided by the main diagonal, include matching data therefore, $x_{ij} = x_{ji}$ where x represents the matrix. Each entry in the adjacency matrix (i, j) represents either a sexual relationship denoted by $x_{ij} = 1$ or a lack of relationship $x_{ij} = 0$.

Density
Density describes the total number of observed edges in a network relative to the total number of possible edges.

Diameter
The diameter of a network is defined as the length of the longest shortest path in a network.

K-core
A *k*-core defines a specific type of component where each node has a minimum degree (the number of connections) of *k* with a minimum degree of 2.

Clique
A clique defines a highly interconnected component of three or more individuals who are directly connected to one another.

Centralization
Centralization measures the extent to which a component represents a centralized structure; whether the network is focused on single node with the highest individual centrality. The term centralization is restricted to component level analysis whereas centrality describes the position of a node within a larger network. Degree, eigenvector, closeness and betweenness centralization determine how centralized a component is

around the node with the highest measure of centrality (each measure of centrality is defined below).

Centrality
Network centrality identifies a nodes position within a component. Higher centrality scores indicate a node is serving as a highly central individual in a component.

Degree centrality
Degree centrality defines the number of relationships surrounding a node. More specifically, degree centrality defines the number of sexual partners an individual has.

Eigenvector Centrality
Eigenvector centrality weights the connection of a focal node with adjacent nodes based on the centrality of the adjacent nodes. Therefore, the entire network is considered when computing eigenvector centrality and reflects the degree to which a node is connected to other parts of the network with high connectivity

Two-reach Centrality
Two-reach centrality defines the number of nodes two steps away from the focal node.

Closeness Centrality
Closeness centrality defines the mean distance a node is from every other node included in the component.

Betweenness Centrality
Betweenness centrality is viewed as the extent to which an individual serves as a channel of STI transmission between two otherwise unconnected individuals.

Radial Structures
Network structures with high centralization around the node with the highest degree. Radial structures with complete centralization are referred to as star components.

Linear Structures
Network structures where individuals are in sequence with one another.